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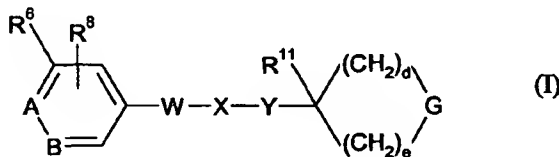
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(54) Title: G PROTEIN COUPLED RECEPTOR (GPR16) AGONISTS AND USE THEREOF FOR TREATING OBESITY AND DIABETES



(57) Abstract: Compounds of formula (I), or pharmaceutically acceptable salts thereof, are agonists of GPR16 and are useful for the treatment of obesity, and for the treatment of diabetes.

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## G-PROTEIN COUPLED RECEPTOR (GPR116) AGONISTS AND USE THEREOF FOR TREATING OBESITY AND DIABETES

## BACKGROUND OF THE INVENTION

The present invention is directed to G-protein coupled receptor (GPCR) agonists. In particular, the present invention is directed to agonists of GPR1 16 that are useful for the treatment of obesity, e.g. as regulators of satiety, and for the treatment of diabetes.

Obesity is characterized by an excessive adipose tissue mass relative to body size. Clinically, body fat mass is estimated by the body mass index (BMI; weight(kg)/height(m)<sup>2</sup>), or waist circumference. Individuals are considered obese when the BMI is greater than 30 and there are established medical consequences of being overweight. It has been an accepted medical view for some time that an increased body weight, especially as a result of abdominal body fat, is associated with an increased risk for diabetes, hypertension, heart disease, and numerous other health complications, such as arthritis, stroke, gallbladder disease, muscular and respiratory problems, back pain and even certain cancers.

Pharmacological approaches to the treatment of obesity have been mainly concerned with reducing fat mass by altering the balance between energy intake and expenditure. Many studies have clearly established the link between adiposity and the brain circuitry involved in the regulation of energy homeostasis. Direct and indirect evidence suggest that serotonergic, dopaminergic, adrenergic, cholinergic, endocannabinoid, opioid, and histaminergic pathways in addition to many neuropeptide pathways (e.g. neuropeptide Y and melanocortins) are implicated in the central control of energy intake and expenditure. Hypothalamic centres are also able to sense peripheral hormones involved in the maintenance of body weight and degree of adiposity, such as insulin and leptin, and fat tissue derived peptides.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidaemia and hyperglycaemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) which is characterized by hypertension and its associated pathologies including atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with decreased insulin sensitivity which can lead to abnormal blood sugar levels when challenged. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

GPR1 16 is a GPCR identified as SNORF25 in WO00/50562 which discloses both the human and rat receptors, US 6,468,756 also discloses the mouse receptor (accession numbers: AAN95194 (human), AAN95195 (rat) and ANN95196 (mouse)).

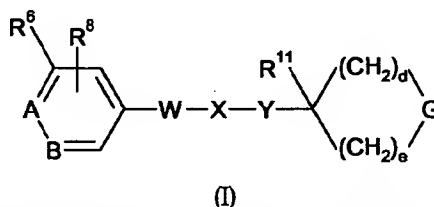
In humans, GPR1 16 is expressed in the pancreas, small intestine, colon and adipose tissue. The expression profile of the human GPR1 16 receptor indicates its potential utility as a target for the treatment of obesity and diabetes.

International patent application WO2005/061489 (published after the priority date of the present application) discloses heterocyclic derivatives as GPR1 16 receptor agonists.

The present invention relates to agonists of GPR1 16 which are useful for the treatment of obesity, e.g. as regulators of satiety, and for the treatment of diabetes.

#### SUMMARY OF THE INVENTION

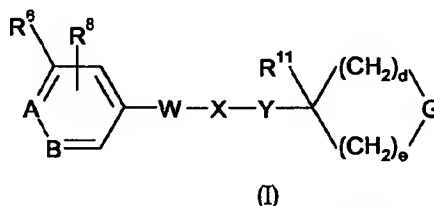
Compounds of formula (I):



or pharmaceutically acceptable salts thereof, are agonists of GPR1 16 and are useful for the prophylactic or therapeutic treatment of obesity, and for the treatment of diabetes.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:



wherein one of A and B is nitrogen and the other is CR<sup>1</sup>;

W and Y are independently a bond, an unbranched or a branched C<sub>1-3</sub> alkylene or an unbranched or a branched C<sub>2-3</sub> alkenylene;

X is selected from CH<sub>2</sub>, O, S, CH(OH), CH(halogen), C(O), C(O)O, C(O)S, SC(O), C(O)CH<sub>2</sub>S, C(O)CH<sub>2</sub>C(OH), C(O)CH<sub>2</sub>C(O), OC(O), NR<sup>5</sup>, CH(NR<sup>5</sup>R<sup>55</sup>), C(O)NR<sup>2</sup>, S(O) and S(O)<sub>2</sub>;

G is CHR<sup>3</sup>, N-C(O)OR<sup>4</sup>, N-C(O)NR<sup>4</sup>R<sup>5</sup>, N-C<sup>alkylene</sup>-C<sup>OR</sup> <sup>4</sup>, N-C(O)C(O)OR<sup>4</sup>, N-S(O)<sub>2</sub>R<sup>4</sup>, N-C(O)R<sup>4</sup> or N-P(O)(O-Ph)<sub>2</sub>; or N-heterocyclyl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy or halogen;

R<sup>1</sup> is hydrogen, halogen, cyano, C(O)NH<sub>2</sub>, C<sub>1-4</sub>alkyl, SO<sub>2</sub>C<sub>1-4</sub>alkyl, SOC<sub>1-4</sub>alkyl or SC<sub>1-4</sub>alkyl;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub>alkyl;

R<sup>3</sup> is C<sub>3-6</sub>alkyl;

R<sup>4</sup> is C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl or C<sub>2-8</sub>alkynyl, any of which may be optionally substituted by one or more halo atoms, NR<sup>5</sup>R<sup>55</sup>, OR<sup>5</sup>, C(O)OR<sup>5</sup>, OC(O)R<sup>5</sup> or cyano, and may contain a CH<sub>2</sub> group that is replaced by O or S; or a C<sub>3-7</sub>cycloalkyl, aryl, heterocyclyl, heteroaryl, C<sub>1-4</sub>alkyleneC<sub>3-7</sub>cycloalkyl, C<sub>1-4</sub>alkylenearyl, C<sub>1-4</sub>alkyleneheterocyclyl or C<sub>1-4</sub>alkyleneheteroaryl, any of which may be substituted with one or more substituents selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>fluoroalkyl, OR<sup>5</sup>, CN, NR<sup>5</sup>R<sup>55</sup>, SO<sub>2</sub>Me, NO<sub>2</sub> or C(O)OR<sup>5</sup>;

R<sup>5</sup> and R<sup>55</sup> are independently hydrogen or C<sub>1-4</sub>alkyl; or taken together R<sup>5</sup> and R<sup>55</sup> may form a 5 or 6 membered heterocyclic ring;

$R^6$  is hydrogen, halogen, CN,  $d$ -alkyl,  $C^a$ alkoxy, ethynyl,  $C(O)NR^7R^{77}$  or  $Ci_{1-4}alkyleneS(O)_e$ ;

$R^7$  and  $R^{77}$  are independently hydrogen or  $C_{1-4}alkyl$ ; or taken together  $R^7$  and  $R^{77}$  may form a 5 or 6 membered heterocyclic ring;

$R^8$  is hydrogen, halogen, CN,  $C_{1-4}alkyl$  or  $C_{1-4}alkoxy$ ;

$R^{11}$  is hydrogen or hydroxy;

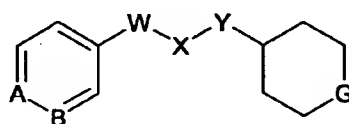
$d$  is 0, 1, 2 or 3;

$e$  is 1, 2, 3, 4 or 5;

with the proviso that  $d + e$  is 2, 3, 4 or 5; and

$f$  is 0, 1 or 2.

In one embodiment of the invention the compound of formula (I) is a compound of formula (Ia), or a pharmaceutically acceptable salt thereof:



(Ia)

wherein one of A and B is nitrogen and the other is  $CR^1$ ;

W and Y are independently a bond,  $C_{1-3}alkylene$  or  $C_{2-3}alkenylene$ ;

X is selected from  $CH_2$ , O, S, CO,  $CO_2$ , COS, SCO,  $COCH_2S$ ,  $COCH_2CO$ , OCO,  $CONR^2$ , SO and  $SO_2$ ;

G is  $CHR^3$ ,  $NCOOR^4$ , or  $NCONR^4R^5$ ;

$R^1$  is hydrogen, halogen, cyano or  $C_{1-4}alkyl$ ;

$R^2$  is  $C_{1-4}alkyl$ ;

$R^3$  is  $C_{3-6}alkyl$ ;

$R^4$  is  $C_{1-6}alkyl$ ,  $C_{2-6}alkenyl$  or  $C_{2-6}alkynyl$  optionally substituted by one or more fluoro atoms or cyano,  $C_{3-7}cycloalkyl$ , or aryl optionally substituted with  $C_{1-4}alkyl$ ,  $C_{1-4}alkoxy$ , halogen,  $CF_3$ , nitro, cyano, or  $CO_2C_{1-4}alkyl$ ; and

$R^5$  is hydrogen or  $C_{1-4}alkyl$ .

The molecular weight of the compounds of formula (I) is preferably less than 800, more preferably less than 600, even more preferably less than 500.

A is preferably nitrogen.

B is preferably  $CR^1$ .

In certain embodiments of the invention -W-X-Y- represents a chain of 2 to 6 atoms in length. -W-X-Y- preferably represents a 4 or 5 atom chain.

When W is  $C_{2-3}alkenylene$ , the stereochemistry at the double bond is preferably (E).

X is preferably  $CH_2$ , O or  $NR^5$ .

Exemplary G groups include,  $CHR^3$ ,  $N-C(O)OR^4$ ,  $N-C(O)NR^4R^5$ ,  $N-C_{1-4}alkylene-C(O)OR^4$ ,  $N-C(O)C(O)OR^4$  and N-heteroaryl. G is preferably  $N-C(O)OR^4$ ,  $N-C(O)NR^4R^5$ ,  $N-C_{1-4}alkylene-C(O)OR^4$ ,  $N-C(O)C(O)OR^4$ , N-heterocyclyl, N-heteroaryl,  $N-S(O)_2R^4$ ,  $N-C(O)R^4$  or  $N-P(O)(O-Ph)_2$ ; especially  $N-C(O)OR^4$ ,  $N-C(O)NR^4R^5$ ,  $N-C_{1-4}alkylene-C(O)OR^4$ , N-heteroaryl,  $N-S(O)_2R^4$  or  $N-C(O)R^4$ ; in particular  $N-C(O)OR^4$ ,  $N-C(O)NR^4R^5$ , N-heteroaryl,  $N-S(O)_2R^4$  or  $N-C(O)R^4$ . More preferably, G is  $N-C(O)OR^4$ ,  $N-C(O)NR^4R^5$  or N-heteroaryl. G is

most preferably NCOOR<sup>4</sup>. When G is N-heteroaryl the heteroaryl ring is preferably pyrimidinyl or pyridinyl, especially pyrimidinyl e.g. pyrimidin-2-yl.

Exemplary R<sup>1</sup> groups include hydrogen, CN, halogen for example chloro or bromo, and C<sub>1-4</sub>alkyl. R<sup>1</sup> is preferably chloro, C<sub>1-4</sub>alkyl, hydrogen or cyano, for example R<sup>1</sup> is C<sub>1-4</sub>alkyl, hydrogen or cyano, especially methyl.

R<sup>2</sup> is preferably C<sub>1-4</sub>alkyl. Exemplary R<sup>2</sup> groups include methyl.

Exemplary R<sup>3</sup> groups include pentyl.

Exemplary R<sup>4</sup> groups include methyl, ethyl, propyl, iso-propyl, sec-butyl, tert-butyl, butynyl, cyclobutyl, pentyl, 2,2-dimethylpropyl, cyclopentyl, hexyl, cyclohexyl, trifluoroethyl, trichloroethyl, phenyl, methoxyphenyl, tolyl, fluorophenyl, chlorophenyl, trifluoromethylphenyl, nitrophenyl, naphthalenyl, chlorobenzyl, methylsulfanylethyl- and tetrahydrofuranmethyl-.

Preferably R<sup>4</sup> represents C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl or C<sub>2-8</sub>alkynyl optionally substituted by one or more halo atoms or cyano, and may contain a CH<sub>2</sub> group that is replaced by O or S; or a C<sub>3-7</sub>cycloalkyl, aryl or C<sub>1-4</sub>alkylC<sub>3-7</sub>cycloalkyl, any of which may be substituted with one or more substituents selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>fluoroalkyl, OR<sup>5</sup>, CN, NR<sup>5</sup>R<sup>55</sup>, NO<sub>2</sub> or C(O)OC<sub>1-4</sub>alkyl. More preferably R<sup>4</sup> represents C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl or C<sub>2-8</sub>alkynyl optionally substituted by one or more halo atoms or cyano, and may contain a CH<sub>2</sub> group that is replaced by O or S; or a C<sub>3-7</sub>cycloalkyl or aryl, either of which may be substituted with one or more substituents selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>fluoroalkyl, OR<sup>5</sup>, CN, NR<sup>5</sup>R<sup>55</sup>, NO<sub>2</sub> or C(O)OC<sub>1-4</sub>alkyl. Most preferred R<sup>4</sup> groups are C<sub>3-5</sub>alkyl optionally substituted by one or more halo atoms or cyano, which may contain a CH<sub>2</sub> group that is replaced by O or S, or C<sub>3-5</sub>cycloalkyl optionally substituted by C<sub>1-4</sub>alkyl. In one embodiment of the invention the group represented by R<sup>4</sup> is unsubstituted.

Exemplary R<sup>5</sup> groups include hydrogen and methyl.

Preferably R<sup>6</sup> is hydrogen, halogen, CN, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, ethynyl or C<sub>1-4</sub>alkyleneS(O)<sub>r</sub>. More preferably R<sup>6</sup> is hydrogen, methyl or halogen, especially hydrogen or methyl.

In one embodiment of the invention d + e is 2, 3, or 4. In a preferred embodiment of the invention d and e each represent 1. In a more preferred embodiment of the invention d and e each represent 2.

Examples of independent R<sup>7</sup> and R<sup>77</sup> groups include hydrogen and methyl, especially hydrogen. An example of a heterocyclic group where R<sup>7</sup> and R<sup>77</sup> are taken together is piperidine.

R<sup>8</sup> is preferably hydrogen or halogen e.g. fluoro. In one embodiment R<sup>8</sup> is hydrogen.

Preferably R<sup>11</sup> represents hydrogen.

When B represents nitrogen, suitably X does not represent C(O)NR<sup>2</sup>.

When -W-X-Y- represents -NHC<sub>0-4</sub>alkyl-, suitably R<sup>4</sup> is C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl or C<sub>2-8</sub>alkynyl, any of which may be optionally substituted by one or more halo atoms, NR<sup>5</sup>R<sup>55</sup>, OR<sup>5</sup>, C(O)OR<sup>5</sup>, OC(O)R<sup>5</sup> or cyano, and which may contain a CH<sub>2</sub> group that is replaced by O or S; or a C<sub>3-7</sub>cycloalkyl, heterocyclyl, C<sub>1-4</sub>alkyleneC<sub>3-7</sub>cycloalkyl or C<sub>1-4</sub>alkyleneheterocyclyl, any of which may be substituted with one or more substituents selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>fluoroalkyl, OR<sup>5</sup>, CN, NR<sup>5</sup>R<sup>55</sup>, SO<sub>2</sub>Me, NO<sub>2</sub> or C(O)OR<sup>5</sup>.

When X represents C(O)NR<sup>2</sup>, preferably W is not a bond or alternatively Y is a bond or contains at least two carbon atoms linking X to the heterocyclic ring.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in formula (I) is selected from the preferred, more preferred or particularly listed groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred and particularly listed groups.

Specific compounds of the invention which may be mentioned are those included in the Examples and pharmaceutically acceptable salts thereof.

As used herein, unless stated otherwise, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkenyl, alkynyl, and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains having at least one unsaturated carbon-carbon bond.

The term "fluoroalkyl" includes alkyl groups substituted by one or more fluorine atoms, e.g.  $\text{CH}_2\text{F}$ ,  $\text{CHF}_2$  and  $\text{CF}_3$ .

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes monocyclic and bicyclic saturated and partially saturated carbocycles. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Examples of partially saturated cycloalkyl groups include cyclohexene and indane. Cycloalkyl groups will typically contain 3 to 10 ring carbon atoms in total (e.g. 3 to 6, or 8 to 10).

The term "halo" includes fluorine, chlorine, bromine, and iodine atoms.

The term "aryl" includes phenyl and naphthyl, in particular phenyl.

Unless otherwise indicated the term "heterocyclyl" and "heterocyclic ring" includes 4- to 10-membered monocyclic and bicyclic saturated rings, e.g. 4- to 7-membered monocyclic saturated rings, containing up to three heteroatoms selected from N, O and S. Examples of heterocyclic rings include oxetane, tetrahydrofuran, tetrahydropyran, oxepane, oxocane, thietane, tetrahydrothiophene, tetrahydrothiopyran, thiepane, thiocane, azetidine, pyrrolidine, piperidine, azepane, azocane, [1,3]dioxane, oxazolidine, piperazine, and the like. Other examples of heterocyclic rings include the oxidised forms of the sulfur-containing rings. Thus, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, tetrahydrothiopyran 1-oxide, and tetrahydrothiopyran 1,1-dioxide are also considered to be heterocyclic rings.

Unless otherwise stated, the term "heteroaryl" includes mono- and bicyclic 5- to 10-membered, e.g. monocyclic 5- or 6-membered, heteroaryl rings containing up to 4 heteroatoms selected from N, O and S. Examples of such heteroaryl rings are furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. Bicyclic heteroaryl groups include bicyclic heteroaromatic groups where a 5- or 6-membered heteroaryl ring is fused to a phenyl or another heteroaromatic group. Examples of such bicyclic heteroaromatic rings are benzofuran, benzothiophene, indole, benzoxazole, benzothiazole, indazole, benzimidazole, benzotriazole, quinoline, isoquinoline, quinazoline, quinoxaline and purine.

Compounds described herein may contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved

enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above formula (I) is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of formula (I) and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically drawn or stated otherwise.

When the compound of formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

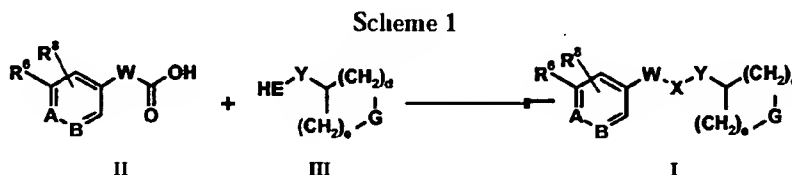
The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include arginine, betaine, caffeine, choline, *N*'*JF*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, *N*-ethylmorpholine, *N*-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

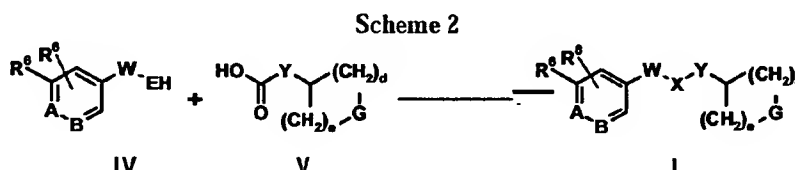
Since the compounds of formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The compounds of formula (I) can be prepared as described below, in which R<sup>6</sup>, R<sup>8</sup>, A, B, d, e, W, X, Y and G are as defined above and which are illustrated in the schemes below for compounds where R<sup>11</sup> is hydrogen.

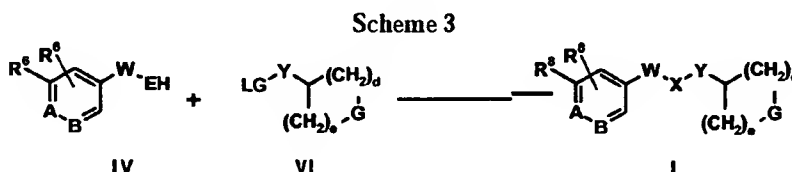
Compounds of formula (I) in which X is CO<sub>2</sub>, COS, or CONR<sup>2</sup> can be prepared by condensing the appropriate acid (II) with an alcohol, thiol, or amine (III), as shown in Scheme 1 where E is O, S, or NR<sup>2</sup>, using a typical reagent for such a condensation reaction, e.g., EDCI (Pottorf, R. S.; Szeto, P. In *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: Chichester, 1999; pp 186-188). The acids (II) and alcohols, thiols, and amines (III) are either commercially available or are prepared easily using known techniques.



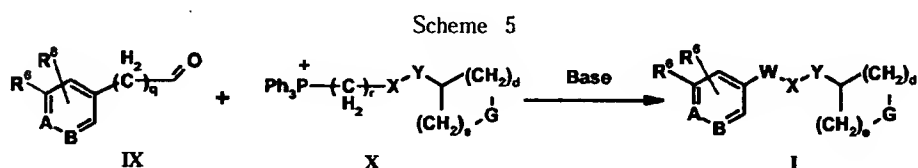
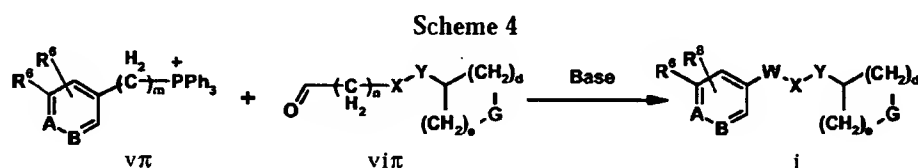
Compounds of formula (I) in which X is SCO or OCO can be prepared by condensing the appropriate thiol or alcohol (FV) with the appropriate acid (V), as shown in Scheme 2 where E is S or O, employing a reagent typically used for effecting such reactions, e.g., EDCI (Pottorf, R. S.; Szeto, P. In *Handbook of Reagents for Organic Synthesis: Activating Agents and Protecting Groups*; Pearson, A. J., Roush, W. R., Eds.; Wiley: Chichester, 1999; pp 186-188). The alcohols and thiols (FV), as well as acids (V), are either commercially available or are prepared straightforwardly using known techniques.



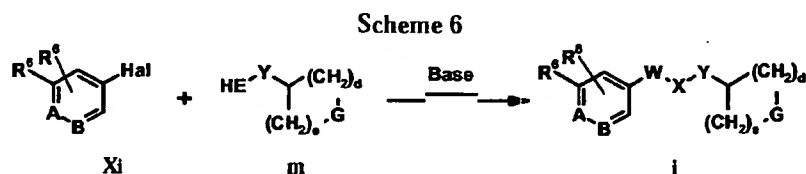
Compounds of formula (I) in which X is S or O can be prepared by alkylating the appropriate thiol or alcohol (IV) with the appropriate alkyl halide or sulfonate ester (VI), as shown in Scheme 3 where E is S or O and LG is chloro, bromo, iodo, alkanesulfonate, or arenesulfonate. The reaction is typically carried out using a base, e.g., potassium tert-butoxide (Hall, S. E., et al. *J. Med. Chem.* 1989, 32, 974-984). The alcohols and thiols (IV), as well as the alkyl halides or sulfonates (VI), are either commercially available or are made easily using known techniques. The compounds of formula (I) where X is SO or SO<sub>2</sub> can easily be obtained from the compounds of formula (I) where X is S by oxidation with, for example, wCPBA (Fyfe, M. C. T. et al. International Patent Publication WO 04/72031).



Compounds of formula (I) in which W is  $C_{2-3}$  alkenylene can be prepared by a Wittig reaction between the appropriate phosphonium salt (VII) and the appropriate aldehyde (VIII), as indicated in Scheme 4 where m is 1 or 2 and n is 0 or 1 with the proviso that  $m + n < 3$ . As an alternative, to the approach described in Scheme 4, the compounds of formula (I) in which W is  $C_{2-3}$  alkenylene can be prepared by a Wittig reaction between the appropriate aldehyde (EX) and the appropriate phosphonium salt (X), as indicated in Scheme 5 where q is 0 or 1 and r is 1 or 2 with the proviso that  $q + r < 3$ . The reactions are carried out in the presence of a suitable base, e.g., NaOMe or LiHMDS (March, J. *Advanced Organic Chemistry*, 4th edn.; Wiley: New York, 1992; pp 956-963). The phosphonium salts (VII) and (X), as well as the aldehydes (VIII) and (EX), are either commercially available or are made easily using known techniques. The compounds of formula (I) where W is  $C_{2-3}$  alkylene can easily be synthesized from the compounds of formula (I) where W is  $C_{2-3}$  alkenylene by a hydrogenation reaction using, for example, palladium on charcoal as a catalyst.



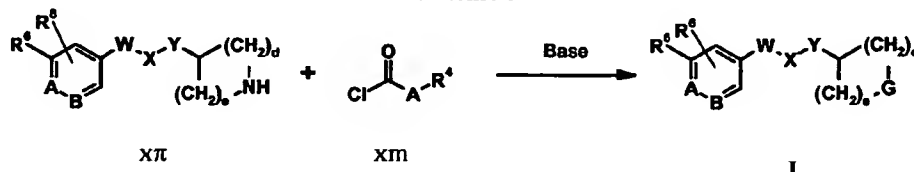
Compounds of the formula (I) where W is a bond, X is S or O, and A is N or C- $R^1$  where  $R^1$  is CN can be prepared by condensation of the appropriate heteroaryl halide (XI), where with the appropriate alcohol or thiol (III), as depicted in Scheme 6 where Hal represents a halogen and E is S or O. The reaction is carried out in the presence of a suitable basic system, e.g., potassium hydroxide and potassium carbonate in the presence of tris(3,6-dioxahexyl)amine (Ballesteros, P.; Claramunt, R. M.; Elguero, J. *Tetrahedron* 1987, 43, 2557-2564). The heteroaryl halides (XI) and alcohols/thiols (III) are either commercially available or are made easily using known techniques.



Compounds of the formula (I) where G is  $NC(O)OR^4$ ,  $NC(O)NR^4R^5$ ,  $NC(O)R^4$ , or  $N-C(O)C(O)OR^4$  can be prepared by the route shown in Scheme 7, where an amine of formula (XII) is condensed with an acyl chloride of formula (XIII) where A is O,  $NR^5$ , a bond, or  $C(O)O$ . The reaction is carried out in the presence of a suitable base, such as triethylamine (Picard, F., et

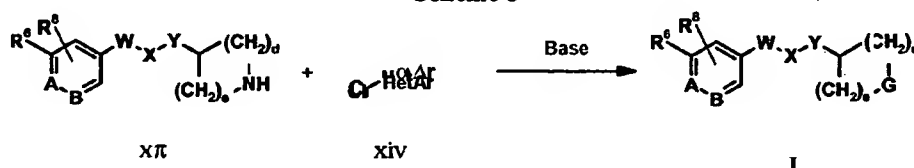
al. *J. Med. Chem.* 2002, 45, 3406-3417). Compounds of the formula (I) where G is  $\text{NCONR}^4\text{R}^5$  and  $\text{R}^5$  is hydrogen may also be prepared by reacting the amine (XII) with a suitable isocyanate  $\text{O}=\text{C}=\text{N}-\text{R}^4$  (Boswell, R. F., Jr., et al. *J. Med. Chem.* 1974, 17, 1000-1008). Compounds of the formula (I) where G is  $\text{N}-\text{C}_{1-4}\text{alkylene}-\text{C}(\text{O})\text{OR}^4$  may be prepared by alkylating the amine (XII) with the appropriate  $\alpha$ -haloester (Rooney, C. S. et al. *J. Med. Chem.* 1983, 26, 700-714). The amine (XII) is generally derived from its *N*-tert-butoxycarbonyl precursor — prepared by one of the routes outlined in Schemes 1-6 — by deprotection with an acid, e.g., trifluoroacetic acid (Fyfe, M. C. T. et al. International Patent Publication WO 04/72031).

Scheme 7



Compounds of the formula (I) where G is N-heteroaryl may be prepared by condensation of amine (XII) with a heteroaryl chloride of formula (XIV), as illustrated in Scheme 8 (Barillari, C. et al. *Eur. J. Org. Chem.* 2001, 4737-741; Birch, A. M. et al. *J. Med. Chem.* 1999, 42, 3342-3355).

Scheme 8



Compounds of the formula (I) where  $\text{R}^1$  is CN can be prepared from the corresponding unsubstituted pyridine by the Reissert reaction (Fife, W. K. *J. Org. Chem.* 1983, 48, 1375-1377). Similar reactions can be used to prepare the compounds where  $\text{R}^1$  is a halogen (Walters, M. A.; Shay, J. J. *Tetrahedron Lett.* 1995, 36, 7575-7578). The compounds where  $\text{R}^1$  is halogen can be transformed into the corresponding compounds where  $\text{R}^1$  is  $\text{C}_{1-4}$  alkyl by transition metal-catalysed cross-coupling reactions (Füster, A., et al. *J. Am. Chem. Soc.* 2002, 124, 13856-13863).

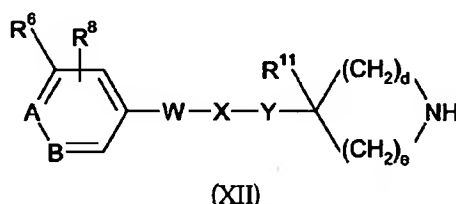
Other compounds of formula (I) may be prepared by methods analogous to those described above or by methods known *per se*.

Further details for the preparation of the compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000, compounds and more preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial "split and mix" approach or by multiple parallel synthesis using either solution or solid phase chemistry, using procedures known to those skilled in the art.

During the synthesis of the compounds of formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of formula (I) or may be present on the final compound of formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2<sup>nd</sup> edition.

Any novel intermediates, such as those defined above, may be of use in the synthesis of compounds of formula (I) and are therefore also included within the scope of the invention, for example compounds of formula (XII):



wherein the groups A, B, W, X, Y, d, e, R<sup>6</sup> and R<sup>8</sup> are as defined above for compounds of formula (I).

A further embodiment of the invention relates to compounds of formula (XII) wherein the groups R<sup>6</sup> and R<sup>8</sup> represent hydrogen, d and e each represent 2 and the groups A, B, W, X and Y are as defined above for compounds of formula (Ia).

As indicated above the compounds of formula (I) are useful as GPRI 16 agonists, e.g. for the treatment and/or prophylaxis of obesity and diabetes. For such use the compounds of formula (I) will generally be administered in the form of a pharmaceutical composition.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, the invention also provides a pharmaceutical composition for the treatment of disease by modulating GPRI 16, resulting in the prophylactic or therapeutic treatment of obesity, e.g. by regulating satiety, or for the treatment of diabetes, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of formula (I), or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions may optionally comprise other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds of formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous).

Thus, the pharmaceutical compositions can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound of formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total

composition. Unit dosage forms will generally contain from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, using a compound of formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of formula (I), or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, obesity may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time

of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of formula (I) may be used in the treatment of diseases or conditions in which GPR1 16 plays a role.

Thus the invention also provides a method for the treatment of a disease or condition in which GPR1 16 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof. Diseases or conditions in which GPR1 16 plays a role include obesity and diabetes. In the context of the present application the treatment of obesity is intended to encompass the treatment of diseases or conditions such as obesity and other eating disorders associated with excessive food intake e.g. by reduction of appetite and body weight, maintenance of weight reduction and prevention of rebound and diabetes (including Type 1 and Type 2 diabetes, impaired glucose tolerance, insulin resistance and diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts, cardiovascular complications and dyslipidaemia). And the treatment of patients who have an abnormal sensitivity to ingested fats leading to functional dyspepsia. The compounds of the invention may also be used for treating metabolic diseases such as metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels and hypertension.

The invention also provides a method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of diabetes, including Type 1 and Type 2 diabetes, particularly type 2 diabetes, comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a method for the treatment of metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of a condition as defined above.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a condition as defined above.

In the methods of the invention the term "treatment" includes both therapeutic and prophylactic treatment.

The compounds of formula (I), or pharmaceutically acceptable salts thereof, may be administered alone or in combination with one or more other therapeutically active compounds. The other therapeutically active compounds may be for the treatment of the same disease or condition as the compounds of formula (I) or a different disease or condition. The

therapeutically active compounds may be administered simultaneously, sequentially or separately.

The compounds of formula (I) may be administered with other active compounds for the treatment of obesity and/or diabetes, for example insulin and insulin analogs, gastric lipase inhibitors, pancreatic lipase inhibitors, sulfonyl ureas and analogs, biguanides,  $\alpha 2$  agonists, glitazones, PPAR- $\gamma$  agonists, mixed PPAR- $\alpha/\gamma$  agonists, RXR agonists, fatty acid oxidation inhibitors,  $\alpha$ -glucosidase inhibitors,  $\beta$ -agonists, phosphodiesterase inhibitors, lipid lowering agents, glycogen phosphorylase inhibitors, antiobesity agents e.g. pancreatic lipase inhibitors, MCH-I antagonists and CB-I antagonists (or inverse agonists), amylin antagonists, lipoxxygenase inhibitors, somostatin analogs, glucokinase activators, glucagon antagonists, insulin signalling agonists, PTPIB inhibitors, gluconeogenesis inhibitors, antilypolitic agents, GSK inhibitors, galanin receptor agonists, anorectic agents, CCK receptor agonists, leptin, serotonergic/dopaminergic antiobesity drugs, reuptake inhibitors e.g. sibutramine, CRF antagonists, CRF binding proteins, thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-I inhibitors or sorbitol dehydrogenase inhibitors.

Combination therapy comprising the administration of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and at least one other antiobesity agent represents a further aspect of the invention.

The present invention also provides a method for the treatment of obesity in a mammal, such as a human, which method comprises administering an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent, to a mammal in need thereof.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent for the treatment of obesity.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with another antiobesity agent, for the treatment of obesity.

The compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s) may be co-administered or administered sequentially or separately.

Co-administration includes administration of a formulation which includes both the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s), or the simultaneous or separate administration of different formulations of each agent. Where the pharmacological profiles of the compound of formula (I), or a pharmaceutically acceptable salt thereof, and the other antiobesity agent(s) allow it, coadministration of the two agents may be preferred.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent in the manufacture of a medicament for the treatment of obesity.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and another antiobesity agent, and a pharmaceutically acceptable carrier. The invention also encompasses the use of such compositions in the methods described above.

GPRI 16 agonists are of particular use in combination with centrally acting antiobesity agents.

The other antiobesity agent for use in the combination therapies according to this aspect of the invention is preferably a CB-I modulator, e.g. a CB-I antagonist or inverse agonist. Examples of CB-I modulators include SR141716 (rimonabant) and SLV-319 ((4S)-(-)-3-(4-chlorophenyl)-*N*-methyl-*N*-[(4-chlorophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide); as well as those compounds disclosed in EP576357, EP656354, WO 03/018060, WO 03/020217, WO 03/020314, WO 03/026647, WO 03/026648, WO 03/027076, WO 03/040105, WO 03/051850, WO 03/051851, WO 03/053431, WO 03/063781, WO 03/075660, WO 03/077847, WO 03/078413, WO 03/082190, WO 03/082191, WO 03/082833, WO 03/084930, WO 03/084943, WO 03/086288, WO 03/087037, WO 03/088968, WO 04/012671, WO 04/013120, WO 04/026301, WO 04/029204, WO 04/034968, WO 04/035566, WO 04/037823, WO 04/052864, WO 04/058145, WO 04/058255, WO 04/060870, WO 04/060888, WO 04/069837, WO 04/069837, WO 04/072076, WO 04/072077, WO 04/078261 and WO 04/108728, and the references disclosed therein.

Other diseases or conditions in which GPR1 16 has been suggested to play a role include those described in WO 00/50562 and US 6,468,756, for example cardiovascular disorders, hypertension, respiratory disorders, gestational abnormalities, gastrointestinal disorders, immune disorders, musculoskeletal disorders, depression, phobias, anxiety, mood disorders and Alzheimer's disease.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

The invention will now be described by reference to the following examples which are for illustrative purposes and are not to be construed as a limitation of the scope of the present invention.

## EXAMPLES

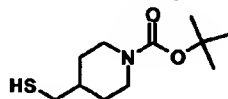
### Materials and methods

Column chromatography was carried out on SiO<sub>2</sub> (40-63 mesh) unless specified otherwise. LCMS data were obtained as follows: Atlantis 3μ C<sub>18</sub> column (3.0 x 20.0 mm, flow rate = 0.85 mL/min) eluting with a H<sub>2</sub>O-CH<sub>3</sub>CN solution containing 0.1% HCO<sub>2</sub>H over 6 min with UV detection at 220 nm. Gradient information: 0.0-0.3 min 100% H<sub>2</sub>O; 0.3-4.25 min: Ramp up to 10% H<sub>2</sub>O-90% CH<sub>3</sub>CN; 4.25-4.4 min: Ramp up to 100% CH<sub>3</sub>CN; 4.4-9.9 min: Hold at 100% CH<sub>3</sub>CN; 9.9-6.0 min: Return to 100% H<sub>2</sub>O. The mass spectra were obtained using an electrospray ionisation source in either the positive (ES<sup>+</sup>) or negative (ES<sup>-</sup>) ion modes. Jones reagent was prepared according to the method described by Meinwald J., et al. *Org Synthesis, Coll. Vol. V*, 866.

Abbreviations and acronyms: Ac: Acetyl; Boc: *tert*-Butoxycarbonyl; *t*-Bu: *tert*-Butyl; 18C6: 18-Crown-6; DIPEA: *N,N*-Diisopropylethylamine; DMAP: 4-(Dimethylamino)pyridine; DMF: *N,N*-Dimethylformamide; EDCI: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Et: Ethyl; HOBt: 1-Hydroxybenzotriazole; IH: Isohexane; wCPBA: 3-Chloroperoxybenzoic acid; Me: Methyl; Ph: Phenyl; RP-HPLC: Reverse phase-high performance liquid chromatography; RT: Retention time; TFA: Trifluoroacetic acid; THF: Tetrahydrofuran. The syntheses of the following compounds have been described elsewhere: 4-(3-Bromo-2-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester: Piotrowski, D. W., et al.

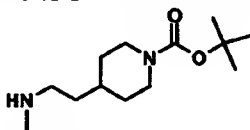
WO 04/013137; 4-(3-Bromopropyl)pyridine hydrobromide: Elpern R., et al., *J. Am. Chem. Soc.* 1957, 79, 1951-1954; 3-(2-Cyanopyridin-4-yl)propyl acetate: Ornstein, P. L., et al. *J. Med. Chem.* 1991, 34, 90-97; 4-Mercaptopiperidine-1-carboxylic acid *tert*-butyl ester: Bru-Magniez, N., et al. US Patent 5,317,025; 4-(2-Methanesulfonyloxyethyl)piperidine-1-carboxylic acid *tert*-butyl ester: Cain, G. A., et al. US Patent 5,252,586; 4-Methylaminomethylpiperidine-1-carboxylic acid *tert*-butyl ester: Hiscock, S. D., et al. WO 03/049737; 4-(2-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester: Piotrowski, D. W., et al. WO 04/013137; 4-(3-Oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester: Keenan, R. M., et al. *J. Med. Chem.* 1999, 42, 545-559; 4-Pentylcyclohexanecarboxylic acid amide: Obikawa, T.; Dcukawa, S., JP 03133963; Pyridin-4-ylmethylphosphonic acid diethyl ester: Hutchison A. J. et al., *J. Med. Chem.*, 1989, 32, 2171-2178; 2-(4-Pyridyl)ethanethiol: Hayashi, H.; Hayashi, K., US Patent 6,720,426; 3-Pyridin-4-ylpropane-1-thiol: Burgess, D. M.; Bayer, H. O., *J. Org. Chem.* 1963, 28, 2283-2288; Triphenylpyridin-4-ylmethylphosphonium bromide: Carsky, P., et al. *Liebigs Ann.* 1980, 291-304. AU other compounds were available from commercial sources.

**Preparation 1:** 4-Mercaptomethylpiperidine-1-carboxylic acid *tert*-butyl ester



A stirred solution of *N*-*tert*-butoxycarbonyl-4-(4-toluenesulfonyloxymethyl)piperidine (240 mg, 0.65 mmol) and thiourea (99 mg, 1.30 mmol) in EtOH (1 mL) was heated under gentle reflux for 16 h. The solvent was evaporated off under reduced pressure to furnish the tosylate salt of 4-carbamimidoylsulfanylmethylpiperidine-1-carboxylic acid *tert*-butyl ester:  $m/z$  ( $ES^+$ ) = 274.0  $[M+H]^+$ . A solution of this salt (250 mg, 0.56 mmol) in H<sub>2</sub>O (1 mL) and concentrated aqueous NH<sub>3</sub> (2 mL) was heated to 100 °C with stirring for 20 min. On cooling, the mixture was partitioned between Et<sub>2</sub>O (30 mL) and H<sub>2</sub>O (10 mL). The pH of the aqueous phase was adjusted to 7 using 2 M HCl and saturated aqueous NaHCO<sub>3</sub>. The organic phase was extracted with 1 M NaOH (15 mL), then the aqueous extracts were neutralised to pH 7 with 2 M HCl. The cloudy mixture was extracted with Et<sub>2</sub>O (50 mL), then the organic extracts were washed with brine (10 mL) and dried (MgSO<sub>4</sub>). Filtration and solvent evaporation furnished the title compound:  $\delta_H$  (CDCl<sub>3</sub>) 1.05-1.20 (m, 2H), 1.35 (t, 1H), 1.48 (s, 9H), 1.50-1.60 (m, 1H), 1.80-1.90 (m, 2H), 2.40-2.50 (m, 2H), 2.60-2.80 (m, 2H), 4.05-4.25 (m, 2H).

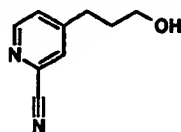
**Preparation 2:** 4-(2-Methylaminoethyl)piperidine-1-carboxylic acid *tert*-butyl ester



MeNH<sub>2</sub> (1.41 mL of a 2.0 M solution in THF, 2.82 mmol) was added to a stirred solution of 4-(2-oxoethyl)piperidine-1-carboxylic acid *tert*-butyl ester (639 mg, 2.81 mmol) in anhydrous PhMe (2 mL). After 30 min, the solution was concentrated in vacuo, then anhydrous THF (2 mL) and anhydrous MeOH (2 mL) were added. The stirred solution was treated with NaBH<sub>4</sub> (128 mg, 3.38 mmol). After 3 h, the solvents were removed under reduced pressure and the residue partitioned between EtOAc (25 mL) and H<sub>2</sub>O (20 mL). The organic layer was washed

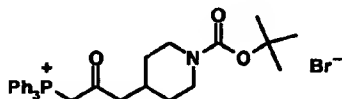
with brine (20 mL), dried ( $\text{MgSO}_4$ ), filtered, and concentrated to furnish the title compound:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.00-1.10 (m, 2H), 1.35-1.45 (m, 10H), 1.50-1.65 (m, 4H), 2.39 (s, 3H), 2.50-2.70 (m, 4H), 3.90-4.10 (m, 2H).

**Preparation 3: 4-(3-Hydroxypropyl)pyridine-2-carbonitrile**



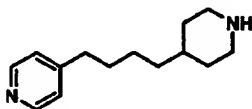
A solution of  $\text{K}_2\text{CO}_3$  (1.67 g, 12.1 mmol) in  $\text{H}_2\text{O}$  (30 mL) was added to a stirred solution of 3-(2-cyanopyridin-4-yl)propyl acetate (4.94 g, 24.2 mmol) in MeOH (130 mL). After 25 min, the MeOH was removed under reduced pressure, then the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried ( $\text{MgSO}_4$ ), filtered, and concentrated to give a residue that was purified by column chromatography (IH-EtOAc, 1:3) to furnish the title compound:  $m/z$  ( $\text{ES}^+$ ) = 163.1  $[\text{M} + \text{H}]^+$ .

**Preparation 4: [3-(1-*tert*-Butoxycarbonylpiperidin-4-yl)-2-oxopropyl]triphenylphosphonium bromide**



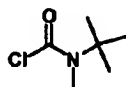
A solution of 4-(3-bromo-2-oxopropyl)piperidine-1-carboxylic acid *tert-butyl* ester (320 mg, 1.0 mmol) and  $\text{PPh}_3$  (267 mg, 1.0 mmol) in anhydrous THF (10 mL) was heated under reflux with stirring for 3 h. The solvent was removed under reduced pressure, then the residue was dissolved in a MeCN-PhMe solution. The solvents were evaporated off in vacuo to give a solid that was triturated with  $\text{Et}_2\text{O}$ . The solid was filtered and washed with more  $\text{Et}_2\text{O}$  to furnish the title compound:  $\delta_{\text{H}}$  ( $\text{CD}_3\text{CN}$ ) 1.00-1.10 (m, 2H), 1.20-1.30 (m, 1H), 1.46 (s, 9H), 1.50-1.57 (m, 2H), 2.65-2.80 (m, 4H), 3.95-4.05 (m, 2H), 5.03 (d, 2H), 7.70-7.80 (m, 12H), 7.85-7.95 (m, 3H).

**Preparation 5: 4-(4-Piperidin-4-ylbutyl)pyridine**



TFA (10 mL) was added over 2 min to a stirred solution of 4-(4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert-butyl* ester (Example 53, 1.13 g, 3.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (15 mL). After 1 h at 20  $^\circ\text{C}$ , the mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (180 mL). The solution was washed with 1 M NaOH (30 mL) and brine (30 mL), before being dried ( $\text{MgSO}_4$ ), filtered, and evaporated. The residue was taken up in EtOAc (5 mL) and filtered through celite. Solvent evaporation furnished the title compound:  $m/z$  ( $\text{ES}^+$ ) = 219.2  $[\text{M} + \text{H}]^+$ .

**Preparation 6: *tert*-Butylmethylcarbamoyl chloride**



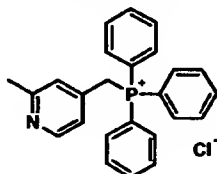
Anhydrous pyridine (162  $\mu\text{L}$ , 2.0 mmol) was added to a vigorously stirred solution of triphosgene (208 mg, 0.7 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL). *tert*-Butylmethanamine (240  $\mu\text{L}$ , 2.0 mmol) was added, then the mixture was stirred at 20  $^\circ\text{C}$  for 3 d. The  $\text{CH}_2\text{Cl}_2$  was removed at 20 $^\circ\text{C}$ /230 mmHg, then  $\text{Et}_2\text{O}$  (20 mL) was added. The precipitated solids were removed by filtration, then the  $\text{Et}_2\text{O}$  was evaporated at 20 $^\circ\text{C}$ /250 mmHg to furnish the title compound:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.45 (s, 9H), 3.15 (s, 3H).

The compounds listed in Table 1 were prepared from the corresponding alcohols using methods similar to that described in Example 59

Table 1

Prep	Structure	Name	RT (min)	$m/z$ ( $\text{ES}^+$ )
7		4-[4-(2-Cyanopyridin-4-yl)-4-trimethylsilanyloxybutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.61	432.4 $[M + H]^+$
8		4-[4-(2-Cyanopyridin-4-yl)-2-trimethylsilanyloxybutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.82	432.2 $[M + H]^+$
9		4-[4-(2-Cyanopyridin-4-yl)-1-trimethylsilanyloxybutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.42	432.2 $[M + H]^+$

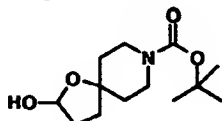
**Preparation 10:** (2-Methylpyridin-4-ylmethyl)triphenylphosphonium chloride



Thionyl chloride (13.64 mL, 187 mmol) was added slowly over 10 min to an ice-cooled, stirred solution of (2-methylpyridin-4-yl)methanol (1.314 g, 10.68 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (60

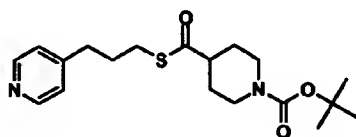
mL). After warming to room temperature and stirring for a further 1.5 h, toluene (50 mL) was added followed by sufficient saturated aqueous  $\text{Na}_2\text{CO}_3$  to achieve pH 10 in the aqueous phase. The aqueous component was separated and extracted further with toluene (2 x 30 mL). The combined organic phases were dried ( $\text{MgSO}_4$ ), sodium iodide (200 mg) and triphenylphosphine (8.40 g, 32.0 mmol) were added, and the solvent volume reduced to 10 mL. The stirred mixture was heated at  $60^\circ\text{C}$  for 48 h, cooled and the solid collected by filtration. This was washed with ether (10 mL) and air-dried to give the title phosphonium salt:  $\delta_{\text{H}}$  (DMSO) 2.26 (s, 3H), 5.20 (d, 2H), 6.70 (s, 1H), 6.82 (d, 1H), 7.70-7.79 (m, 12H), 7.91-7.94 (m, 3H), 8.30 (d, 1H).

**Preparation 11:** 2-Hydroxy-1-oxa-8-azaspiro[4.5]decane-8-carboxylic acid *tert*-butyl ester



A stirred solution of 4-hydroxy-4-(3-hydroxypropyl)piperidine-1-carboxylic acid *tert*-butyl ester (1.0 g, 3.86 mmol) in  $\text{CH}_2\text{Cl}_2$  (60 mL) was cooled on an ice bath and Dess-Martin periodinane (1.8 g, 4.24 mmol) added. After 1 h, the reaction mixture was diluted with ether (120 mL) and washed with 2 M aqueous NaOH (70 mL). The aqueous phase was extracted with ether (60 mL) and the combined organic phases washed with water (50 mL) and brine (50 mL) then dried ( $\text{MgSO}_4$ ). The solvent was removed and the residue purified by column chromatography (1H-EtOAc 3:2) to afford the title compound:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.48 (s, 9H), 1.48-1.62 (m, 2H), 1.62-1.77 (m, 3H), 1.91-2.08 (m, 3H), 3.35 (m, 2H), 3.56 (m, 2H), 5.51 (d, 1H).

**Example 1:** 4-(3-Pyridin-4-ylpropylsulfanylcarbonyl)piperidine-1-carboxylic acid *tert*-butyl ester



A mixture of 1-(*tert*-butoxycarbonyl)isonipecotic acid (90 mg, 390  $\mu\text{mol}$ ) and EDCI (94 mg, 490  $\mu\text{mol}$ ) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3 mL) was stirred for 30 min, before being treated with a solution of DMAP (8 mg, 65  $\mu\text{mol}$ ) and 3-pyridin-4-ylpropane-1-thiol (50 mg, 326  $\mu\text{mol}$ ) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1 mL). After 20 h, the reaction mixture was concentrated to ca. 1 mL, then  $\text{Et}_2\text{O}$  (2 mL) was added. The solvent was decanted from the resulting gum which was chromatographed ( $\text{Et}_2\text{O}$ ) to provide the title compound: RT = 3.49 min; *m/z* ( $\text{ES}^+$ ) = 365.0 [ $\text{M} + \text{H}$ ] $^+$ .

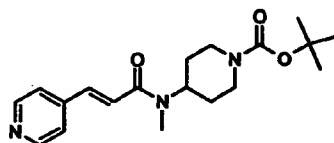
The compounds shown in Table 2 were prepared by condensation of a thiol or alcohol with the appropriate acid and employed protocols similar to those described in Example 1.

Table 2

Eg	Structure	Name	RT (min)	m/z (ES <sup>+</sup> )
2		4-Pentylcyclohexane carbothioic acid S-(3-pyridin-4-ylpropyl) ester	4.52	334.0 [M + H] <sup>+</sup>
3		4-(2-Pyridin-4-ylethylsulfanyl carbonyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.87	351.2 [M + H] <sup>+</sup>
4		4-Pentylcyclohexane carbothioic acid S-(2-pyridin-4-ylethyl) ester	4.22	320.2 [M + H] <sup>+</sup>
5		4-(Pyridine-4-carbonylsulfanyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.84	323.0 [M + H] <sup>+</sup>
6		( <i>E</i> )-4-(3-Pyridin-4-ylacryloylsulfanyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.61	349.0 [M + H] <sup>+</sup>
7		4-(3-Pyridin-4-ylpropionylsulfanyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.11	351.0 [M + H] <sup>+</sup>
8		4-(Pyridine-4-carbonylsulfanyl methyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.92	321.9 [M + 2H + MeCN - <i>t</i> - Bu] <sup>+</sup>
9		4-(3-Pyridin-4-ylpropionyl sulfanylmethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.99	365.0 [M + H] <sup>+</sup>
10		4-(2-Pyridin-4-ylacetoxymethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.17	335.0 [M + H] <sup>+</sup>
11		4-(2-Pyridin-4-ylacetoxypiperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.15	321.0 [M + H] <sup>+</sup>

Eg	Structure	Name	RT (min)	m/z (ES <sup>+</sup> )
12		4-[3-(2-Pyridin-4-ylacetoxy)propyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.31	363.0 [M + H] <sup>+</sup>
13		Isonicotinic acid 3-(1- <i>tert</i> -butoxycarbonylpiperidin-4-yl)propyl ester	4.32	349.0 [M + H] <sup>+</sup>
14		( <i>E</i> )-4-(3-Pyridin-4-ylacryloyloxymethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.56	347.0 [M + H] <sup>+</sup>
15		( <i>E</i> )-4-(3-Pyridin-4-ylacryloyloxy)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.45	332.9 [M + H] <sup>+</sup>
16		( <i>E</i> )-4-[3-(3-Pyridin-4-ylacryloyloxy)propyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.94	375.0 [M + H] <sup>+</sup>
17		4-(2-Pyridin-4-ylethoxy carbonylmethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.97	349.0 [M + H] <sup>+</sup>
18		Piperidine-1,4-dicarboxylic acid 1- <i>tert</i> -butyl ester 4-(2-pyridin-4-ylethyl) ester	2.64	335.1 [M + H] <sup>+</sup>
19		Piperidine-1,4-dicarboxylic acid 1- <i>tert</i> -butyl ester 4-(3-pyridin-4-ylpropyl) ester	2.67	349.1 [M + H] <sup>+</sup>

Example 20: (E)-4-[Methyl(3-pyridin-4-ylacryloyl)amino]piperidine-1-carboxylic acid *tert*-butyl ester



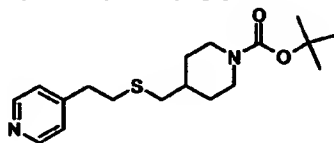
A mixture of (E)-3-pyridin-4-ylacrylic acid (100 mg, 671  $\mu\text{mol}$ ), EDCI (133 mg, 671  $\mu\text{mol}$ ), HOBT (91 mg, 671  $\mu\text{mol}$ ),  $\text{NEt}_3$  (94  $\mu\text{L}$ , 671  $\mu\text{mol}$ ), and anhydrous  $\text{CH}_2\text{Cl}_2$  (3 mL) was stirred for 20 min, before being treated with 1-*tert*-butoxycarbonyl-4-methylaminopiperidine (131 mg, 610  $\mu\text{mol}$ ). After 3 d, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (2 mL), before being washed with  $\text{H}_2\text{O}$  (10 mL), saturated aqueous  $\text{NaHCO}_3$  (10 mL), and brine (10 mL). The  $\text{CH}_2\text{Cl}_2$  solution was dried ( $\text{MgSO}_4$ ), filtered, and concentrated. The residue was purified by RP-HPLC to furnish the title compound: RT = 2.81 min; *m/z* ( $\text{ES}^+$ ) = 346.2 [ $\text{M} + \text{H}$ ] $^+$ .

The compounds shown in Table 3 were prepared by condensation of the appropriate acid with an amine utilising protocols similar to those described in Example 20.

Table 3

Eg	Structure	Name	RT (min)	<i>m/z</i> ( $\text{ES}^+$ )
21		4-{2-[Methyl(pyridine-4-carbonyl)amino]ethyl}piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.15	348.2 [ $\text{M} + \text{H}$ ] $^+$
22		4-[Methyl(pyridine-4-carbonyl)amino]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.87	639.4 [ $2\text{M} + \text{H}$ ] $^+$
23		4-{2-[Methyl(2-pyridin-4-ylacetyl)amino]ethyl}piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.72	362.2 [ $\text{M} + \text{H}$ ] $^+$
24		4-{2-[Methyl(3-pyridin-4-ylacryloyl)amino]ethyl}piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.99	374.2 [ $\text{M} + \text{H}$ ] $^+$
25		4-{[Methyl-(3-pyridin-4-ylacryloyl)amino]methyl}piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.76	360.2 [ $\text{M} + \text{H}$ ] $^+$

Example 26: 4-(2-Pyridin-4-ylethylsulfanylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester



A stirred solution of 2-(4-pyridyl)ethanethiol (213 mg, 1.53 mmol) in anhydrous THF (2 mL) was treated with *t*-BuOK (63 mg, 0.56 mmol). 4-Methanesulfonyloxymethylpiperidine-

1-carboxylic acid *tert*-butyl ester (150 mg, 0.51 mmol) was added, then the mixture was stirred at 20°C for 1 h, before being heated under reflux. After 18 h, the reaction was cooled to 20°C, diluted with Et<sub>2</sub>O (20 mL) and was washed with saturated aqueous NaHCO<sub>3</sub> (10 mL) and brine (10 mL), before being dried (MgSO<sub>4</sub>). Filtration, solvent evaporation, and column chromatography (EtOAc) provided the title compound: RT = 2.92 min; *m/z* (ES<sup>+</sup>) = 337.1 [M+H]<sup>+</sup>.

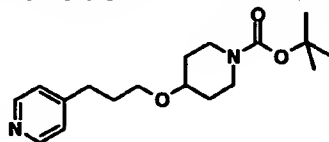
The compounds catalogued in Table 4 were prepared using the *t*-BuOK-mediated alkylation of a pyridine-containing thiol or alcohol with the appropriate piperidine-containing mesylate, as illustrated by Example 26.

Table 4

Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
27		4-(2-Pyridin-4-ylethylsulfanyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.94	323.1 [M+H] <sup>+</sup>
28		4-[2-(2-Pyridin-4-ylethylsulfanyl)ethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.04	351.2 [M+H] <sup>+</sup>
29		4-(3-Pyridin-4-ylpropylsulfanylmethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.79	351.1 [M+H] <sup>+</sup>
30		4-(3-Pyridin-4-ylpropylsulfanyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.84	337.2 [M+H] <sup>+</sup>
31		4-[2-(3-Pyridin-4-ylpropylsulfanyl)ethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.89	365.2 [M+H] <sup>+</sup>
32		4-(2-Pyridin-4-ylethoxymethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.72	321.2 [M+H] <sup>+</sup>
33		4-(3-Pyridin-4-ylpropoxymethyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.72	335.2 [M+H] <sup>+</sup>

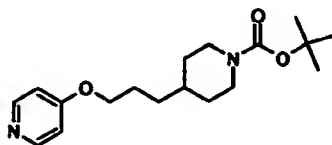
Eg	Structure	Name	RT (min)	m/z (ES <sup>+</sup> )
34		4-[2-(3-Pyridin-4-ylpropoxy)ethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.76	349.2 [M + H] <sup>+</sup>
35		4-[2-(2-Pyridin-4-ylethoxy)ethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.72	335.2 [M + H] <sup>+</sup>
36		4-[3-(2-Cyanopyridin-4-yl)propoxymethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.05	260.2 [M - Boc + 2H] <sup>+</sup>
37		4-{2-[3-(2-Cyanopyridin-4-yl)propoxy]ethyl}piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.12	274.2 [M - Boc + 2H] <sup>+</sup>
38		4-[3-(Pyridin-4-ylmethoxy)propyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.01	335.2 [M + H] <sup>+</sup>
39		4-[2-(2-Bromopyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.99	399.0, 401.0 [M + H] <sup>+</sup>

Example 40: 4-(3-Pyridin-4-ylpropoxy)piperidine-1-carboxylic acid *tert*-butyl ester



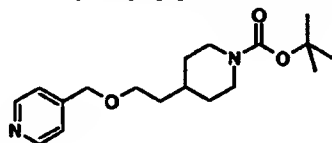
Solid *t*-BuOK 153 mg, 1.36 mmol) was added in one portion to a solution of 4-hydroxypiperidine-1-carboxylic acid *tert*-butyl ester (143 mg, 712  $\mu$ mol) in anhydrous THF (6 mL) followed by 4-(3-bromopropyl)pyridine hydrobromide (200 mg, 712  $\mu$ mol) and tetra-*n*-butylammonium iodide (26 mg, 71  $\mu$ mol). After stirring for 24 h, the reaction mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (20 mL) and brine (20 mL) then dried (MgSO<sub>4</sub>). Removal of the solvent and purification of the residue by column chromatography (1H-EtOAc, 5:1 to 4:1) afforded the title compound: RT = 1.89 min; *m/z* (ES<sup>+</sup>) = 321.3 [M + H]<sup>+</sup>.

Example 41: 4-[3-(Pyridin-4-yloxy)propyl]piperidine-1-carboxylic acid *tert*-butyl ester



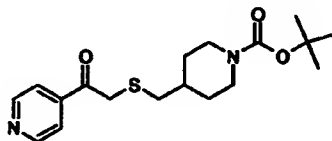
4-Chloropyridine hydrochloride (0.75 g, 5.0 mmol) was added to a stirred suspension of pulverised KOH (1.12 g, 20.0 mmol) and  $K_2CO_3$  (0.69 g, 5.0 mmol) in anhydrous PhMe (50 mL). After 10 min, 4-(3-hydroxypropyl)piperidine-1-carboxylic acid *tert*-butyl ester (1.83 g, 7.5 mmol) and tris(3,6-dioxaheptyl)amine (160  $\mu$ L, 0.5 mmol) were added, then the reaction heated to 120°C for 20 h. On cooling to ambient temperature, the reaction mixture was washed with  $H_2O$  (2 x 15 mL) and brine (20 mL), before being dried ( $MgSO_4$ ). Filtration, solvent evaporation, and column chromatography (IH-EtOAc, 7:3 to 1:4) provided the title compound: RT = 2.82 min; *m/z* ( $ES^+$ ) = 321.2 [ $M^+$  H] $^+$ .

**Example 42:** 4-[2-(Pyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester



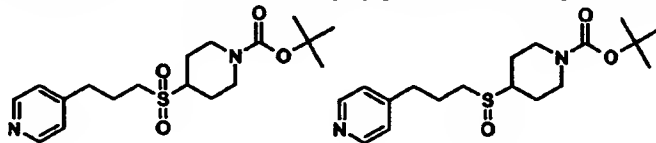
4-Chloromethylpyridine was reacted with 4-(2-hydroxyethyl)piperidine-1-carboxylic acid *tert*-butyl ester using similar conditions to those described in **Example 41** to afford the title compound: RT = 1.99 min; *m/z* ( $ES^+$ ) = 321.3 [ $M^+$  H] $^+$ .

**Example 43:** 4-(2-Oxo-2-pyridin-4-ylethylsulfanylmethyl)piperidine-1-carboxylic acid *tert*-butyl ester



*t*-BuOK (44 mg, 400  $\mu$ mol) was added to a stirred solution of 4-mercaptomethyl piperidine-1-carboxylic acid *tert*-butyl ester (**Preparation 1**, 50 mg, 216  $\mu$ mol) and 2-bromo-1-pyridin-4-ylethanone hydrobromide (121 mg, 432  $\mu$ mol) in anhydrous dioxane (3 mL). After 16 h, the reaction mixture was diluted with EtOAc (70 mL), before being washed with  $H_2O$  (15 mL) and brine (15 mL). After drying ( $MgSO_4$ ), the organic phase was filtered, concentrated, and purified by column chromatography (IH-EtOAc, 1:1) to furnish the title compound: RT = 3.72 min; *m/z* ( $ES^+$ ) = 351.2 [ $M^+$  H] $^+$ .

**Examples 44 and 45:** 4-(3-Pyridin-4-ylpropane-1-sulfonyl)piperidine-1-carboxylic acid *tert*-butyl ester and 4-(3-Pyridin-4-ylpropane-1-sulfinyl)piperidine-1-carboxylic acid *tert*-butyl ester



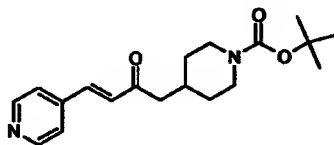
wCPBA (224 mg, 65% pure, 842  $\mu\text{mol}$ ) was added to a stirred solution of 4-(3-pyridin-4-ylpropylsulfanyl)piperidine-1-carboxylic acid *tert*-butyl ester (Example 30, 189 mg, 562  $\mu\text{mol}$ ) in  $\text{CH}_2\text{Cl}_2$  (15 mL). After 2.5 h, the reaction was quenched with saturated aqueous  $\text{Na}_2\text{CO}_3$  (5 mL). The organic layer was washed with brine, dried ( $\text{MgSO}_4$ ), filtered, and concentrated, then the residue purified by column chromatography. The title sulfone eluted first using MeOH-EtOAc (1:19): RT = 2.37 min;  $m/z$  ( $\text{ES}^+$ ) = 369.1  $[\text{M} + \text{H}]^+$ . The title sulfoxide eluted with THF and was further purified by RP-HPLC: RT = 2.32 min;  $m/z$  ( $\text{ES}^+$ ) = 353.1  $[\text{M} + \text{H}]^+$ .

The compounds listed in Table 5 were prepared from the appropriate thioether employing the protocol exemplified by Examples 44 and 45.

Table 5

Eg	Structure	Name	RT (min)	$m/z$ ( $\text{ES}^+$ )
46		4-(3-Pyridin-4-ylpropane-1-sulfonylmethyl) piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.42	383.1 $[\text{M} + \text{H}]^+$
47		4-(3-Pyridin-4-ylpropane-1-sulfinylmethyl) piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.36	367.2 $[\text{M} + \text{H}]^+$
48		4-[2-(3-Pyridin-4-ylpropane-1-sulfonyl)ethyl] piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.62	397.2 $[\text{M} + \text{H}]^+$
49		4-[2-(3-Pyridin-4-ylpropane-1-sulfinyl)ethyl] piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.40	381.2 $[\text{M} + \text{H}]^+$
50		4-(2-Pyridin-4-ylethanesulfonylmethyl) piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.62	369.2 $[\text{M} + \text{H}]^+$

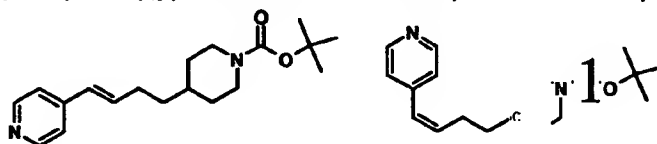
Example 51: (E)-4-(2-Oxo-4-pyridin-4-ylbut-3-enyl)piperidine-1-carboxylic acid *tert*-butyl ester



A solution of NaOMe (85  $\mu\text{L}$  of a 25 wt % solution in MeOH, 372  $\mu\text{mol}$ ) in anhydrous MeOH (3 mL) was added dropwise over 25 min to a mixture of 4-pyridinecarboxaldehyde

(43 mg, 401  $\mu$ mol) and [3-(*tert*-butoxycarbonylpiperidin-4-yl)-2-oxopropyl]triphenylphosphonium bromide (Preparation 4, 200 mg, 343  $\mu$ mol) in anhydrous DMF (7 mL). The mixture was stirred for 23.5 h, the solvents were evaporated under reduced pressure and the residue was partitioned between EtOAc (50 mL) and H<sub>2</sub>O (25 mL). The aqueous phase was extracted with EtOAc (25 mL), then the combined organic extracts were washed with H<sub>2</sub>O (20 mL) and dried (MgSO<sub>4</sub>). Filtration, solvent evaporation, and purification by RP-HPLC afforded the title compound: RT = 3.01 min; *m/z* (ES<sup>+</sup>) = 331.2 [M + H]<sup>+</sup>.

Examples 52 and 53: (E)-4-(4-Pyridin-4-ylbut-3-enyl)piperidine-1-carboxylic acid *tert*-butyl ester and (Z)-4-(4-Pyridin-4-ylbut-3-enyl)piperidine-1-carboxylic acid *tert*-butyl ester

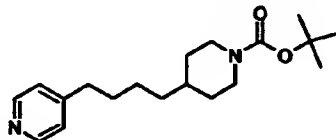


K<sub>2</sub>CO<sub>3</sub> (145 mg, 1.05 mmol) and 18C6 (6 mg, 2.3  $\mu$ mol) were added to a stirred solution of 4-(3-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester (250 mg, 1.04 mmol) and triphenylpyridin-4-ylmethylphosphonium bromide (452 mg, 1.04 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (8 mL). After 20 h, more K<sub>2</sub>CO<sub>3</sub> (23 mg, 0.17 mmol) was added and stirring was continued for an additional 3 h. The mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and H<sub>2</sub>O (10 mL). The organic phase was washed with H<sub>2</sub>O (10 mL), before being dried (MgSO<sub>4</sub>). Filtration, solvent evaporation, and purification by RP-HPLC gave the title (u)-compound:  $\delta_H$  (CDCl<sub>3</sub>) 1.10-1.20 (m, 2H), 1.40-1.50 (m, 12H), 1.70-1.80 (m, 2H), 2.30-2.35 (m, 2H), 2.65-2.80 (m, 2H), 4.05-4.20 (br, 2H), 6.37 (d, 1H), 6.45-6.55 (m, 1H), 7.21 (d, 2H), 8.55 (d, 2H); RT = 3.04 min; and (Z)-compound:  $\delta_H$  (CDCl<sub>3</sub>) 1.05-1.15 (m, 2H), 1.35-1.45 (m, 1H), 1.60-1.80 (m, 3H), 2.30-2.40 (m, 2H), 2.60-2.70 (m, 2H), 4.00-4.20 (br, 2H), 5.80-5.90 (m, 1H), 6.39 (d, 1H), 7.20 (d, 2H), 8.60 (d, 2H); RT = 3.11 min.

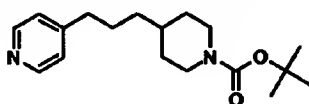
The compounds listed in Table 6 were prepared via a Wittig reaction employing the protocol exemplified by Examples 52 and 53.

Table 6

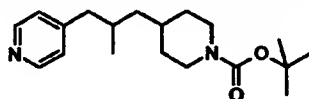
Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
54		(E)-4-(3-Pyridin-4-ylallyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.90	303.2 [M + H] <sup>+</sup>
55		(Z)-4-(3-Pyridin-4-ylallyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.84	303.2 [M + H] <sup>+</sup>

**Example 56:** 4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester

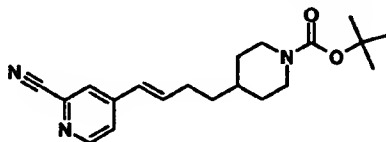
A stirred solution of (Z)-4-(4-pyridin-4-ylbut-3-enyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 53**, 78 mg, 246  $\mu$ mol) in EtOAc (4 mL) was treated with a slurry of Pd (30 mg, 10% on C, 28  $\mu$ mol) in EtOAc (1 mL), before being placed under a  $H_2$  atmosphere. After 4 h, the reaction mixture was filtered through a celite pad, washing with EtOAc (3 x 10 mL). The combined EtOAc solutions were concentrated to afford the title compound: RT = 3.02 min;  $m/z$  ( $ES^+$ ) = 319.3 [ $M+H$ ] $^+$ .

**Example 57:** 4-(3-Pyridin-4-ylpropyl)piperidine-1-carboxylic acid *tert*-butyl ester

(Z)-4-(3-Pyridin-4-ylallyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 55**) was reduced, utilising the protocol outlined above in **Example 56**, to produce the title compound: RT = 2.86 min;  $m/z$  ( $ES^+$ ) = 305.2 [ $M+H$ ] $^+$ .

**Example 58:** 4-(2-Methyl-3-pyridin-4-ylpropyl)piperidine-1-carboxylic acid *tert*-butyl ester

A solution of pyridin-4-ylmethylphosphonic acid diethyl ester (229 mg, 1 mmol) in anhydrous THF (4 mL) was treated with sodium hydride (40 mg of a 60% dispersion in oil, 1 mmol). After 10 min, a solution of 4-(2-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester (241 mg, 1 mmol) in anhydrous THF (2 mL) was introduced and the reaction mixture stirred for 1 h at room temperature then at 70°C for 3 h. On cooling, the reaction was poured into water (10 mL) and extracted with EtOAc (2 x 40 mL). The organic phase was washed with brine (20 mL), dried ( $MgSO_4$ ) and evaporated. The residue was purified by column chromatography (H-EtOAc, 2:1) to afford a mixture of (*E*)- and (Z)-4-(2-methyl-3-pyridin-4-ylallyl)piperidine-1-carboxylic acid *tert*-butyl ester: RT = 2.07 min;  $m/z$  ( $ES^+$ ) = 317.4 [ $M+H$ ] $^+$ . A solution of this mixture of olefins was reduced using the procedure described in **Example 56** to give the title compound: RT = 2.26 min;  $m/z$  ( $ES^+$ ) = 319.4 [ $M+H$ ] $^+$ .

**Example 59:** (E)-4-[4-(2-Cyanopyridin-4-yl)but-3-enyl]piperidine-1-carboxylic acid *tert*-butyl ester

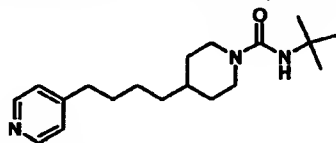
A solution of (E)-4-(4-(4-pyridin-4-yl)but-3-enyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 52**, 101 mg, 318  $\mu$ mol) and wCPBA (78 mg, 70% pure, 318  $\mu$ mol) in  $\text{CH}_2\text{Cl}_2$  (4 mL) was stirred at 20 °C for 3 h. More wCPBA (12 mg, 70% pure, 49  $\mu$ mol) was added, then the mixture was stirred for a further 45 min, before being purified by column chromatography (EtOAc then THF) to furnish (E)-4-[4-(1-oxypyridin-4-yl)but-3-enyl]piperidine-1-carboxylic acid *tert*-butyl ester:  $m/z$  ( $\text{ES}^+$ ) = 333.2 [ $M + \text{H}$ ] $^+$ . A mixture of this *N*-oxide (106 mg, 318  $\mu$ mol),  $\text{Me}_3\text{SiCN}$  (170  $\mu$ L, 1275  $\mu$ mol) and  $\text{NEt}_3$  (90  $\mu$ L, 644  $\mu$ mol) was heated at 100 °C for 1 h. On cooling to ambient temperature, the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated aqueous  $\text{NaHCO}_3$  (10 mL),  $\text{H}_2\text{O}$  (10 mL), and brine (10 mL). The organic phase was dried ( $\text{MgSO}_4$ ), filtered, concentrated, and purified by column chromatography (1H-EtOAc, 9:1 to 4:1) to yield the title compound: RT = 4.26 min;  $m/z$  ( $\text{ES}^+$ ) = 683.5 [ $2M + \text{H}$ ] $^+$ .

The compounds catalogued in Table 7 were prepared employing protocols similar to that described in **Example 59**.

Table 7

Eg	Structure	Name	RT (min)	$m/z$ ( $\text{ES}^+$ )
60		4-[4-(2-Cyanopyridin-4-yl)butyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.30	288.2 [ $M + 2\text{H} - t\text{-Bu}$ ] $^+$
61		4-[3-(2-Cyanopyridin-4-yl)propyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	4.11	274.1 [ $M + 2\text{H} - t\text{-Bu}$ ] $^+$
62		4-[2-(2-Cyanopyridin-4-yl)methoxy]ethyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.87	346.3 [ $M + \text{H}$ ] $^+$

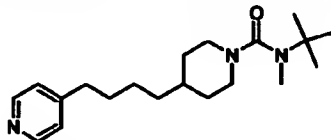
**Example 63:** 4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butylamide



*tert*-Butyl isocyanate (9  $\mu$ L, 75  $\mu$ mol) was added to a stirred solution of 4-(4-piperidin-4-ylbutyl)pyridine (**Preparation 5**, 15 mg, 68  $\mu$ mol) in anhydrous DMF (0.5 mL). After 18 h, the solvent was removed under reduced pressure, then the residue was dissolved in EtOAc (2 mL).

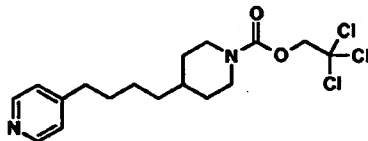
The EtOAc solution was filtered through a short silica plug and evaporated to furnish the title compound: RT = 2.64 min;  $m/z$  ( $ES^+$ ) = 318.3 [ $M + H$ ] $^+$ .

Example 64: 4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid tert-butylmethanamide



A solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 40 mg, 183  $\mu$ mol) in  $CH_2Cl_2$  (1 mL) was added to tert-butylmethylcarbamoyl chloride (Preparation 6, 55 mg, 368  $\mu$ mol). DIPEA (70  $\mu$ L, 400  $\mu$ mol) was added, then the mixture was stirred for 16 h at 20  $^{\circ}C$ . The solvent was removed under reduced pressure, then the residue was purified twice by column chromatography (IH-EtOAc, 1:1) to give the title compound: RT = 2.90 min;  $m/z$  ( $ES^+$ ) = 332.3 [ $M + H$ ] $^+$ .

Example 65: 4-(4-Pyridin-4-yl-butyl)piperidine-1-carboxylic acid 2,2,2-trichloroethyl ester



A solution of 2,2,2-trichloroethyl chloroformate (13  $\mu$ L, 95  $\mu$ mol) in anhydrous  $CH_2Cl_2$  (0.2 mL) was added to a stirred solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 22 mg, 100  $\mu$ mol) and pyridine (8.5  $\mu$ L, 105  $\mu$ mol) in anhydrous  $CH_2Cl_2$  (1 mL). After stirring at room temperature for 18 h, the reaction mixture was diluted with  $Et_2O$  (7 mL) and washed with 2 M aqueous NaOH (2 mL) and water (2 mL). The ethereal solution was then extracted with 1 M aqueous HCl (5 mL) and the aqueous phase basified to pH 9 using saturated aqueous  $Na_2CO_3$ . The resulting mixture was extracted with  $Et_2O$  (15 mL), which was then dried ( $MgSO_4$ ) and evaporated to afford the title compound: RT = 2.38 min;  $m/z$  ( $ES^+$ ) = 393.2 [ $M + H$ ] $^+$ .

The compounds listed in Table 8 were prepared from the appropriate chloroformates using methods similar to that described in Example 65.

Table 8

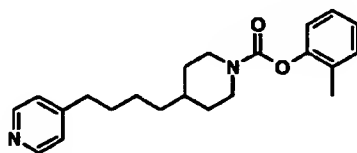
Eg	Structure	Name	RT (min)	$m/z$ ( $ES^+$ )
66		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid isobutyl ester	2.20	319.3 [ $M + H$ ] $^+$

Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
67		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 4-methoxyphenyl ester	2.22	369.3 [ <i>M</i> + H] <sup>+</sup>
68		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2,2-dimethylpropyl ester	2.34	333.3 [ <i>M</i> + H] <sup>+</sup>
69		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid phenyl ester	2.38	339.4 [ <i>M</i> + H] <sup>+</sup>
70		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid cyclopentyl ester	2.39	331.3 [ <i>M</i> + H] <sup>+</sup>
71		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2-chlorobenzyl ester	2.50	387.3 [ <i>M</i> + H] <sup>+</sup>
72		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid <i>p</i> -tolyl ester	2.35	353.3 [ <i>M</i> + H] <sup>+</sup>
73		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid propyl ester	2.06	305.3 [ <i>M</i> + H] <sup>+</sup>
74		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid hexyl ester	2.55	347.4 [ <i>M</i> + H] <sup>+</sup>
75		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid prop-2-ynyl ester	2.09	301.3 [ <i>M</i> + H] <sup>+</sup>

Eg	Structure	Name	RT (min)	m/z (ES <sup>+</sup> )
76		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid naphthalen-1-yl ester	2.58	389.3 [M + H] <sup>+</sup>
77		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 4-fluorophenyl ester	2.34	357.3 [M + H] <sup>+</sup>
78		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 4-methoxycarbonylphenyl ester	2.35	397.3 [M + H] <sup>+</sup>
79		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 4-nitrophenyl ester	3.22	384.4 [M + H] <sup>+</sup>
80		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid isopropyl ester	2.86	305.1 [M + H] <sup>+</sup>
81		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 4-chlorophenyl ester	3.19	373.3 [M + H]
82		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 3-trifluoromethylphenyl ester	3.32	407.5 [M + H] <sup>+</sup>
83		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2-chlorophenyl ester	3.22	373.3 [M + H] <sup>+</sup>

Eg	Structure	Name	RT (min)	$m/z$ ( $ES^+$ )
84		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2-methoxyphenyl ester	3.04	369.3 $[M+H]^+$
85		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid but-2-ynyl ester	2.81	315.2 $[M+H]^+$
86		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid naphthalen-2-yl ester	3.37	389.3 $[M+H]^+$
87		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid pentyl ester	3.27	333.3 $[M+H]^+$

Example 88: 4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid o-tolyl ester



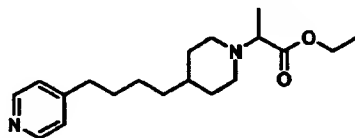
A solution of triphosgene (1.5 mL of a 0.0407 M solution in THF, 61  $\mu$ mol) was added to 2-methylphenol (19.8 mg, 183  $\mu$ mol) under argon and  $NEt_3$  (51  $\mu$ L, 366  $\mu$ mol) in anhydrous THF (0.5 mL) was then introduced. After stirring for 0.5 h, precisely 1.0 mL of the resulting mixture was added to a stirred solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 20 mg, 91.5  $\mu$ mol) in anhydrous THF (1.0 mL). After 0.5 h, the reaction was diluted with EtOAc (12 mL), washed with water (4 mL) and brine (4 mL), then dried ( $MgSO_4$ ). The solvent was evaporated and the residue purified by column chromatography (EtOAc) to afford the title compound: RT = 3.14 min;  $m/z$  ( $ES^+$ ) = 353.2  $[M+H]^+$ .

The compounds listed in Table 9 were synthesised according to procedures similar to that described in Example 88.

Table 9

Eg	Structure	Name	RT (min)	m/z (ES <sup>+</sup> )
89		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2-cyano-1,1-dimethylethyl ester	2.90	344.3 [M + H] <sup>+</sup>
90		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2,2,2-trifluoroethyl ester	2.90	345.1 [M + H] <sup>+</sup>
91		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid cyclobutyl ester	2.86	317.2 [M + H] <sup>+</sup>
92		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid cyclohexyl ester	3.15	345.2 [M + H] <sup>+</sup>
93		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid 2-methylsulfanylethyl ester	2.76	337.1 [M + H] <sup>+</sup>
94		4-(4-Pyridin-4-ylbutyl)piperidine-1-carboxylic acid tetrahydrofuran-2-ylmethyl ester	2.64	347.2 [M + H] <sup>+</sup>

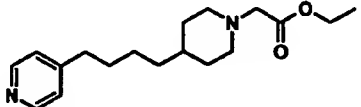
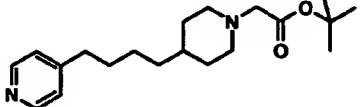
Example 95: 2-[4-(4-Pyridin-4-ylbutyl)piperidin-1-yl]propionic acid ethyl ester



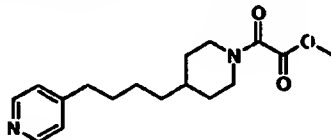
A solution of ethyl-2-bromopropionate in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added to a stirred solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 20 mg, 91.5 μmol) and NEt<sub>3</sub> (19 μL, 140 μmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL). After 18 h, the solvent was evaporated and the residue purified by column chromatography (EtOAc) to afford the title compound: RT = 1.77 min; m/z (ES<sup>+</sup>) 319.2 [M + H]<sup>+</sup>.

The compounds listed in Table 10 were produced using protocols similar to that described in Example 95.

Table 10

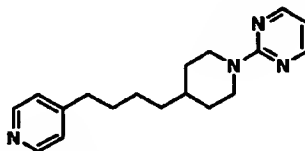
Eg	Structure	Name	RT (min)	$m/z$ (ES <sup>+</sup> )
96		[4-(4-Pyridin-4-ylbutyl)piperidin-1-yl]acetic acid ethyl ester	1.67	305.2 [M + H] <sup>+</sup>
97		[4-(4-Pyridin-4-ylbutyl)piperidin-1-yl]acetic acid <i>tert</i> -butyl ester	1.86	333.2 [M + H] <sup>+</sup>

Example 98: Oxo-[4-(4-pyridin-4-ylbutyl)piperidin-1-yl]acetic acid methyl ester



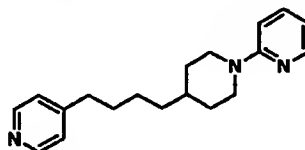
A stirred solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 70 mg, 320  $\mu$ mol) and NEt<sub>3</sub> (89  $\mu$ L, 640  $\mu$ mol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) was treated with neat methyl chlorooxoacetate (31  $\mu$ L, 335  $\mu$ mol). After 5 min the solvent was evaporated and the residue purified by column chromatography (EtOAc) to afford the title compound: RT = 2.24 min;  $m/z$  (ES<sup>+</sup>) = 305.1 [M + H]<sup>+</sup>.

Example 99: 2-[4-(4-Pyridin-4-ylbutyl)piperidin-1-yl]pyrimidine



A solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 20 mg, 91.5  $\mu$ mol), 2-bromopyrimidine (17.5 mg, 110  $\mu$ mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (30  $\mu$ L, 200  $\mu$ mol) in 1,4-dioxane (0.4 mL) was stirred at RT for 52 h. The solvent was removed and the residue purified by column chromatography (EtOAc) to afford the title compound: RT = 2.31 min;  $m/z$  (ES<sup>+</sup>) = 297.1 [M + H]<sup>+</sup>.

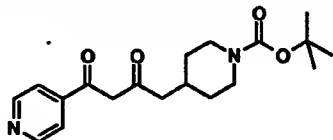
Example 100: 4-(4-Pyridin-4-ylbutyl)-3,4,5,6-tetrahydro-2 *H*-[1,2']bipyridinyl



Neat 1,8-diazabicyclo[5.4.0]undec-7-ene (21.5  $\mu$ L, 140  $\mu$ mol) was added to a solution of 4-(4-piperidin-4-ylbutyl)pyridine (Preparation 5, 21 mg, 96  $\mu$ mol) in 2-fluoropyridine (0.4 mL) and the stirred mixture heated at 80 °C. After 6 h the solvent was removed and the residue

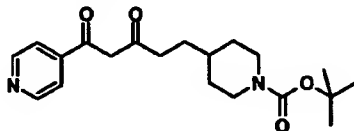
purified by column chromatography (EtOAc) to afford the title compound: RT = 1.99 min;  $m/z$  ( $ES^+$ ) = 296.1 [ $M+H$ ] $^+$ .

**Example 101:** 4-(2,4-Dioxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



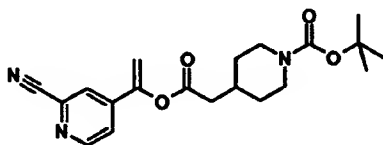
Lithium diisopropylamide (2.16 mL of a 2 M solution in THF, 4.32 mmol) was added to a flask charged with anhydrous THF (15.3 mL). After cooling to  $-78\text{ }^{\circ}\text{C}$ , neat 4-acetylpyridine (0.48 mL, 4.32 mmol) was introduced in a dropwise manner and the resulting solution stirred at  $-78\text{ }^{\circ}\text{C}$  for 45 min. To this mixture was then added slowly *via cannula* solution prepared by adding 1,1'-carbonyldiimidazole (0.666g, 4.11 mmol) in one portion to a solution of 4-carboxymethylpiperidine-1-carboxylic acid *tert*-butyl ester (1 g, 4.11 mmol) in anhydrous THF (7.6 mL) and stirring at room temperature for 45 min. The resulting reaction mixture was slowly brought to RT and stirred for a further 2 h, then diluted with EtOAc (150 mL). The organic phase was washed with 10% aqueous citric acid (2 x 15 mL), saturated aqueous  $\text{NaHCO}_3$  (2 x 15 mL) and brine (15 mL) then dried ( $\text{MgSO}_4$ ). The solvent was removed and the residue purified by RP-HPLC to afford the title compound: RT = 3.72 min;  $m/z$  ( $ES^+$ ) = 347.2 [ $M+H$ ] $^+$ .

**Example 102:** 4-(3,5-Dioxo-5-pyridin-4-yl-pentyl)piperidine-1-carboxylic acid *tert*-butyl ester



4-Acetylpyridine with 4-(2-carboxyethyl)piperidine-1-carboxylic acid *tert*-butyl ester in a manner analogous to that described in Example 101 to give the title compound: RT = 3.87 min;  $m/z$  ( $ES^+$ ) = 361.3 [ $M+H$ ] $^+$ .

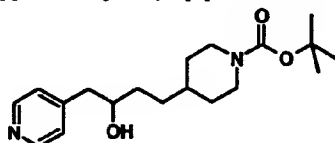
**Example 103:** 4-[1-(2-Cyanopyridin-4-yl)vinyl]oxycarbonylmethyl]piperidine-1-carboxylic acid *tert*-butyl ester



A stirred solution of diisopropylamine (140  $\mu\text{L}$ , 1.03 mmol) in anhydrous THF (2.5 mL) was cooled to  $-10\text{ }^{\circ}\text{C}$  and *n*-butyllithium (410  $\mu\text{L}$  of a 2.5 M solution in hexane, 1.03 mmol) added. After 20 min, the solution was cooled to  $-78\text{ }^{\circ}\text{C}$  and 4-acetylpyridine-2-carbonitrile (150 mg, 1.03 mmol) in anhydrous THF (2.5 mL) was introduced and stirring continued for 45 min. To this was then added a mixture prepared by treating a solution of 4-carboxymethylpiperidine-1-carboxylic acid *tert*-butyl ester (275 mg, 1.13 mmol) and  $\text{NEt}_3$  (160  $\mu\text{L}$ , 1.13 mmol) in dry

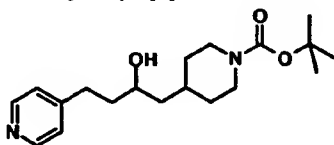
THF (5 mL) at 0 °C with isobutylchloroformate (147  $\mu$ L, 1.6 mmol) and then stirring at room temperature for 1 h. The resulting reaction was allowed to warm to room temperature and, after 18 h, the solvent was evaporated and the residue dissolved in EtOAc (20 mL). The solution was washed with saturated aqueous  $\text{NaHCO}_3$  (5 mL) and brine (5 mL) then dried ( $\text{MgSO}_4$ ) and evaporated. Column chromatography (IH-EtOAc, 7:3) afforded the required compound: RT = 3.84 min;  $m/z$  ( $\text{ES}^+$ ) = 372.07 [ $\text{M} + \text{H}$ ] $^+$ .

**Example 104:** 4-(2-Hydroxy-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



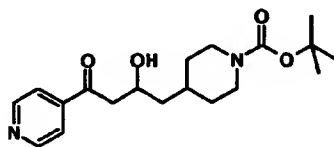
Diisopropylamine (4.1 mL, 29.26 mmol) in anhydrous THF (30 mL) was cooled to -10 °C and *n*-butyllithium (11.25 mL of a 2.5 M solution in hexane, 28.13 mmol) added dropwise. After stirring for 15 min, the solution was cooled to -78 °C and 4-methylpyridine (2.74 mL, 28.13 mmol) in anhydrous THF (25 mL) was introduced slowly over 45 min, ensuring the temperature did not exceed -60 °C during the addition. After again cooling to -78 °C, a solution of 4-(3-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester (4.55 g, 18.85 mmol) in anhydrous THF (25 mL) was added slowly over 25 min then stirred for a further 2 h before being allowed to warm to room temperature. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (20 mL) and diluted with EtOAc (300 mL). The organic phase was separated, washed with brine (30 mL), dried ( $\text{MgSO}_4$ ) then evaporated to dryness. The solvent was removed and the residue purified by column chromatography (IH-EtOAc, 1:4) to furnish the title compound: RT = 1.85 min;  $m/z$  ( $\text{ES}^+$ ) = 335.4 [ $\text{M} + \text{H}$ ] $^+$ .

**Example 105:** 4-(2-Hydroxy-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



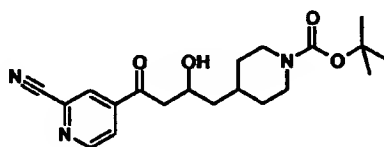
4-Methylpyridine was treated with lithiumdiisopropylamide and then reacted with 4-oxiranylmethylpiperidine-1-carboxylic acid *tert*-butyl ester using a procedure analogous to that described in Example 104 to afford the title compound: RT = 2.57 min;  $m/z$  ( $\text{ES}^+$ ) = 335.3 [ $\text{M} + \text{H}$ ] $^+$ .

**Example 106:** 4-(2-Hydroxy-4-oxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



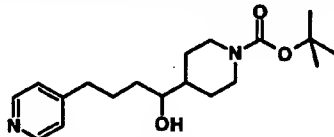
Diisopropylamine (150  $\mu$ L, 1.46 mmol) in anhydrous THF (2 mL) was cooled to 10°C and *n*-butyllithium (560  $\mu$ L of a 2.5 M solution in hexane, 1.40 mmol) was added. After stirring for 15 min, the solution was cooled to -78°C and 1-pyridin-4-ylethanone (154  $\mu$ L, 1.40 mmol) introduced. After 30 min, a solution of 4-(2-oxoethyl)piperidine-1-carboxylic acid *tert*-butyl ester (254 mg, 1.12 mmol) in anhydrous THF (1.5 mL) was added and the reaction stirred for a further 2 h before being quenched with saturated aqueous NaHCO<sub>3</sub> (2 mL). Following dilution with EtOAc (50 mL), the organic phase was separated and dried (MgSO<sub>4</sub>) then evaporated. The residue was purified by column chromatography (EtOAc) to give the title compound: RT = 3.15 min;  $m/z$  (ES<sup>+</sup>) = 349.2 [M+ H]<sup>+</sup>.

**Example 107:** 4-[4-(2-Cyanopyridin-4-yl)-2-hydroxy-4-oxobutyl]piperidine-1-carboxylic acid *tert*-butyl ester



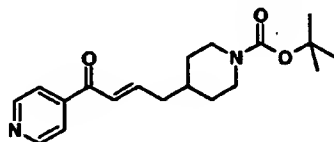
4-Acetylpyridine-2-carbonitrile was reacted with 4-(2-oxoethyl)piperidine-1-carboxylic acid *tert*-butyl ester, using the procedure described in Example 106 to afford the title compound: RT = 3.45 min;  $m/z$  (ES<sup>+</sup>) = 374.1 [M+ H]<sup>+</sup>.

**Example 108:** 4-(1-Hydroxy-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



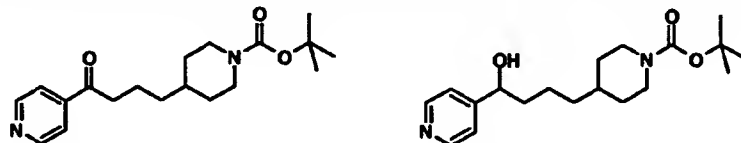
A suspension of 4-(3-bromopropyl)pyridine hydrobromide (297 mg, 1.057 mmol) in Et<sub>2</sub>O (20 mL) was washed with saturated aqueous Na<sub>2</sub>CO<sub>3</sub> (5 mL) and the ethereal solution dried (MgSO<sub>4</sub>) before being concentrated to about 2 mL in volume. Following dilution with hexane (8 mL) the stirred solution was cooled to -78°C and treated with *t*-butyllithium (1.33 mL of a 1.5 M solution in pentane, 2.0 mmol). After 30 min, a solution of 4-formylpiperidine-1-carboxylic acid *tert*-butyl ester in dry Et<sub>2</sub>O (2.0 mL) was added and stirring continued for 1 h. The reaction was then quenched with saturated aqueous NH<sub>4</sub>Cl (2 mL) and diluted with EtOAc (40 mL). After washing the organic phase with brine (5 mL) and drying (MgSO<sub>4</sub>), the solvent was removed and the residue purified by column chromatography (EtOAc-MeOH, 25:1) to give the title compound: RT = 1.83 min;  $m/z$  (ES<sup>+</sup>) = 335.3 [M+ H]<sup>+</sup>.

**Example 109:** (Z)-4-(4-Oxo-4-pyridin-4-ylbut-2-enyl)piperidine-1-carboxylic acid *tert*-butyl ester



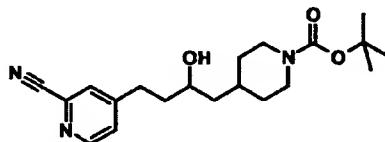
A solution of 4-(2-hydroxy-4-oxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester (Example 106, 124 mg, 356  $\mu$ mol) and  $\text{NEt}_3$  (150  $\mu$ L, 1.07 mmol) was cooled to 0°C and methanesulfonyl chloride (30.5  $\mu$ L, 400  $\mu$ mol) added. After stirring at room temperature for 4 h, the reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and washed with brine (4 mL) and dried ( $\text{MgSO}_4$ ). Evaporation of the solvent and purification of the residue by column chromatography (IH-EtOAc, 1:4) gave the title compound: RT = 3.56 min;  $m/z$  ( $\text{ES}^+$ ) = 331.3 [ $\text{M} + \text{H}$ ] $^+$ .

Examples 110 and 111: 4-(4-Oxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester and 4-(4-hydroxy-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



A slurry of Pd (80 mg, 10% on C, 75  $\mu$ mol) in EtOAc (1 mL) was added to a stirred solution of (Z)-4-(4-oxo-4-pyridin-4-ylbut-2-enyl)piperidine-1-carboxylic acid *tert*-butyl ester (Example 109, 457 mg, 1.385 mmol) in EtOAc (15 mL) and a hydrogen atmosphere introduced. After 2.5 h, the mixture was filtered through a pad of Celite, washing with a little EtOAc, and the solvent evaporated. Purification by column chromatography (IH-EtOAc, 3:7) afforded firstly the title ketone: RT = 3.74 min;  $m/z$  ( $\text{ES}^+$ ) = 333.3 [ $\text{M} + \text{H}$ ] $^+$ , and subsequently the title alcohol: RT = 2.67 min;  $m/z$  ( $\text{ES}^+$ ) = 335.3 [ $\text{M} + \text{H}$ ] $^+$ .

Example 112: 4-[4-(2-Cyanopyridin-4-yl)-2-hydroxybutyl]piperidine-1-carboxylic acid *tert*-butyl ester



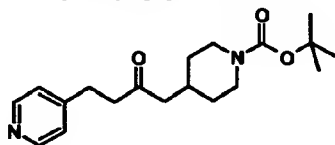
Tetra-*n*-butylammonium fluoride (8.2 mL of a 1 M solution in THF, 8.2 mmol) was added to a stirred solution of 4-[4-(2-cyanopyridin-4-yl)-2-trimethylsilyloxybutyl]piperidine-1-carboxylic acid *tert*-butyl ester (Preparation 8, 3.212 g, 7.452 mmol) in THF (25 mL). After 1 h the reaction was poured into  $\text{Et}_2\text{O}$  (250 mL) and washed with water (25 mL), brine (25 mL) then dried ( $\text{MgSO}_4$ ). The solvent was removed and the residue purified by column chromatography (IH-EtOAc, 3:7) to afford the title compound: RT = 3.47 min;  $m/z$  ( $\text{ES}^+$ ) = 360.2 [ $\text{M} + \text{H}$ ] $^+$ .

The alcohols listed in Table 11 were produced from the corresponding silyl ethers in a manner similar to that described in Example 112.

Table 11

Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
113		4-[4-(2-Cyanopyridin-4-yl)-4-hydroxybutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.72	360.3 [M + H] <sup>+</sup>
114		4-[4-(2-Cyanopyridin-4-yl)-1-hydroxybutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.49	360.2 [M + H] <sup>+</sup>

**Example 115:** 4-(2-Oxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



Jones reagent (1.7 mL) was added at to stirred solution of 4-(2-hydroxy-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 105**, 167 mg, 499  $\mu$ mol) in acetone (4 mL) at 0°C. The reaction mixture was stirred at this temperature for 4.5 h then basified to pH 9 by the careful addition of saturated aqueous Na<sub>2</sub>CO<sub>3</sub>. After dilution with water (2 mL) and EtOAc (20 mL), the precipitated solids were removed by filtration through a pad of Celite. The organic phase was then separated and washed with brine (5 mL), dried (MgSO<sub>4</sub>) and evaporated to give the title compound: RT = 2.56 min; *m/z* (ES<sup>+</sup>) = 333.3 [M + H]<sup>+</sup>.

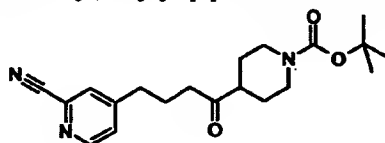
The compounds in Table 12 were synthesised from the corresponding alcohols using procedures similar to that described in Example 115.

Table 12

Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
116		4-(3-Oxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.19	333.4 [M + H] <sup>+</sup>
117		4-(4-Pyridin-4-yl-butyryl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.56	333.4 [M + H] <sup>+</sup>

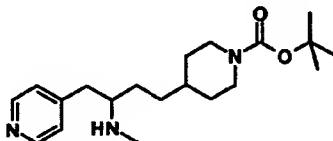
Eg	Structure	Name	RT (min)	$m/z$ ( $ES^+$ )
118		4-[4-(2-Cyanopyridin-4-yl)-2-oxobutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.65	358.2 $[M + H]^+$
119		4-[4-(2-Cyanopyridin-4-yl)butyryl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	3.95	358.2 $[M + H]^+$

Example 120: 4-[4-(2-Cyanopyridin-4-yl)butyryl]piperidine-1-carboxylic acid *tert*-butyl ester



Using a procedure similar to that described in Example 59, 4-(4-pyridin-4-yl-butyryl)piperidine-1-carboxylic acid *tert*-butyl ester was converted to the title compound: RT = 3.74 min;  $m/z$  ( $ES^+$ ) = 358.2  $[M + H]^+$ .

Example 121: 4-(3-Methylamino-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester



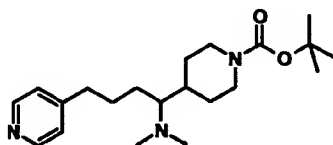
$Ti(O^iPr)_4$  (10?  $\mu L$ , 362  $\mu mol$ ) was added to a stirred solution of  $NEt_3$  (51  $\mu L$ , 362  $\mu mol$ ), 4-(3-oxo-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester (Example 116, 60 mg, 181  $\mu mol$ ) and methylamine hydrochloride (24.4 mg, 362  $\mu mol$ ) in EtOH (1 mL). After 3 h,  $NaBH_4$  (11 mg, 290  $\mu mol$ ) was added and stirring continued for a further 3 h. The reaction mixture was diluted with  $CH_2Cl_2$  (20 mL) and washed with water (4 mL) and brine (4 mL) then dried ( $MgSO_4$ ). Following removal of the solvent, the crude product was purified by column chromatography (MeOH-EtOAc, 1:9 then MeOH-EtOAc- $NEt_3$ , 1:0.5:8.5) to give the title compound: RT = 2.31 min;  $m/z$  ( $ES^+$ ) = 348.3  $[M + H]^+$ .

The compounds listed in Table 13 were synthesised from the corresponding ketones using procedures similar to that described in Example 121.

Table 13

Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
122		4-(1-Methylamino-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.59	373.2 [M + H] <sup>+</sup>
123		4-[4-(2-Cyanopyridin-4-yl)-4-methylaminobutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.79	373.2 [M + H] <sup>+</sup>
124		4-[4-(2-Cyano-pyridin-4-yl)-2-methylaminobutyl]piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.59	373.2 [M + H] <sup>+</sup>

**Example 125:** 4-(1-Dimethylamino-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester

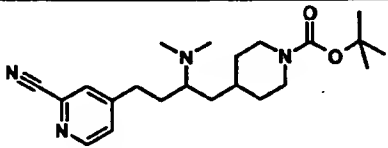


A stirred solution of 4-(1-methylamino-4-pyridin-4-ylbutyl)piperidine-1-carboxylic acid *tert*-butyl ester (**Example 122**, 22 mg, 60  $\mu$ mol), formaldehyde (8 mL of a 37% aqueous solution, 900  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was treated with sodium triacetoxyborohydride (20 mg, 900  $\mu$ mol). After 18 h, the reaction mixture was washed with saturated aqueous NaHCO<sub>3</sub> (2 mL) and dried (MgSO<sub>4</sub>). Evaporation of the solvent afforded the title compound: RT = 2.52 min; *m/z* (ES<sup>+</sup>) = 362.14 [M + H]<sup>+</sup>.

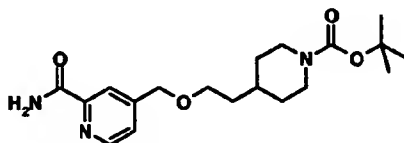
The compounds listed in **Table 14** were synthesised from the corresponding amines using procedures similar to that described in **Example 125**.

**Table 14**

Eg	Structure	Name	RT (min)	<i>m/z</i> (ES <sup>+</sup> )
126		4-[4-(2-Cyanopyridin-4-yl)-4-dimethylaminobutyl]-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.77	387.2 [M + H] <sup>+</sup>

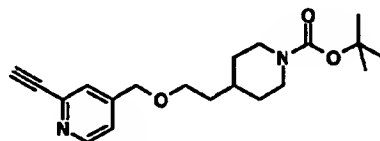
Eg	Structure	Name	RT (min)	m/z (ES <sup>+</sup> )
127		4-[4-(2-Cyanopyridin-4-yl)-2-dimethylaminobutyl]-piperidine-1-carboxylic acid <i>tert</i> -butyl ester	2.62	387.2 [M + H] <sup>+</sup>

Example 128: 4-[2-(2-Carbamoylpyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester



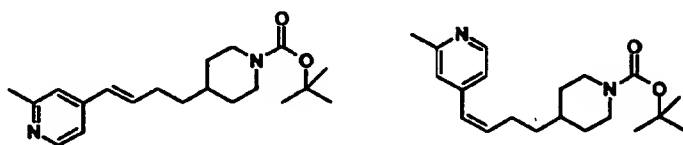
A stirred solution of 4-[2-(2-cyanopyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester (Example 62, 50 mg, 145  $\mu$ mol) in anhydrous THF (3 mL) was treated with methylmagnesium chloride (0.1 mL of a 3 M solution in THF, 300  $\mu$ mol). After 18 h, the reaction mixture was poured into EtOAc (20 mL) and washed with saturated aqueous NH<sub>4</sub>Cl (3 mL) and brine (5 mL). The solvent was removed and column chromatography afforded the title compound: RT = 3.29 min; *m/z* (ES<sup>+</sup>) = 364.1 [M + H]<sup>+</sup>.

Example 129: 4-[2-(2-Ethynylpyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester



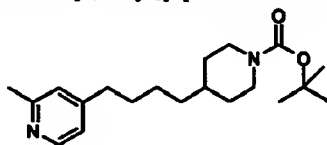
An argon-purged solution of 4-[2-(2-bromopyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester (Example 39, 75 mg, 190  $\mu$ mol) in anhydrous DMF (3 mL) was treated sequentially with NEt<sub>3</sub> (30  $\mu$ L, 215  $\mu$ mol), trimethylsilylacetylene (50  $\mu$ mL, 355  $\mu$ mol), copper(I) iodide (2 mg, 10  $\mu$ mol) and dichlorobis(triphenylphosphine)palladium(II). After stirring 17 h, the same quantities of NEt<sub>3</sub>, trimethylsilylacetylene, copper(I) iodide and dichlorobis(triphenylphosphine)palladium(II) were again added. After 44 h the solvent was removed and the residue purified by column chromatography (IH-EtOAc, 1:1) to afford 4-[2-(2-trimethylsilanylethynylpyridin-4-ylmethoxy)ethyl]piperidine-1-carboxylic acid *tert*-butyl ester: RT = 4.55 min; *m/z* (ES<sup>+</sup>) = 417.1 [M + H]<sup>+</sup>. A mixture of this acetylene in methanol (10 mL) and K<sub>2</sub>CO<sub>3</sub> (45 mg, 325  $\mu$ mol) was stirred for 16 h, the solvent evaporated and the residue purified by column chromatography (IH-EtOAc, 1:1) to give the title compound: RT = 3.74 min; *m/z* (ES<sup>+</sup>) = 345.1 [M + H]<sup>+</sup>.

Examples 133 and 134: 4-[(E)-4-(2-Methylpyridin-4-yl)but-3-enyl]piperidine-1-carboxylic acid *tert*-butyl ester and 4-[(Z)-4-(2-Methylpyridin-4-yl)but-3-enyl]piperidine-1-carboxylic acid *tert*-butyl ester



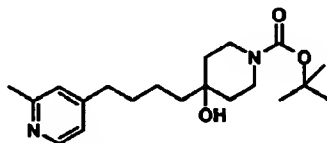
(2-Methylpyridin-4-ylmethyl)triphenylphosphonium chloride (**Preparation 10**) was reacted with 4-(3-oxopropyl)piperidine-1-carboxylic acid *tert*-butyl ester, using a method similar to that described in Examples 52 and 53, to afford the title (E)-olefin:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.12 (dq, 2H), 1.44 (t, 2H), 1.47 (s, 9H), 1.61 (s, 1H), 1.69 (d, 2H), 2.27 (q, 2H), 2.54 (s, 3H), 2.69 (t, 2H), 4.09 (m, 2H), 6.30 (d, 1H), 6.43 (dt, 1H), 7.02 (d, 1H), 7.07 (s, 1H), 8.39 (d, 1H); and the title (Z)-olefin:  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 1.09 (m, 2H), 1.41 (t, 2H), 1.46 (s, 9H), 1.58 (s, 1H), 1.62 (d, 2H), 2.34 (q, 2H), 2.56 (s, 3H), 2.66 (t, 2H), 4.06 (m, 2H), 5.80 (dt, 1H), 6.32 (d, 1H), 6.96 (d, 1H), 7.00 (s, 1H), 8.45 (d, 1H).

**Example 135:** 4-[4-(2-Methylpyridin-4-yl)butyl]piperidine-1-carboxylic acid *tert*-butyl ester



A mixture of (E)- and (Z)- 4-[4-(2-methylpyridin-4-yl)but-3-enyl]piperidine-1-carboxylic acid *tert*-butyl esters (Examples 133 and 134) was hydrogenated over a Pd catalyst, using a similar procedure to that described in Example 56, to afford the title compound: RT = 2.70 min;  $m/z$  ( $\text{ES}^+$ ) = 333.2  $[\text{M} + \text{H}]^+$ .

**Example 136:** 4-Hydroxy-4-[4-(2-methylpyridin-4-yl)butyl]piperidine-1-carboxylic acid *tert*-butyl ester



(2-Methylpyridin-4-ylmethyl)triphenylphosphonium chloride was reacted with 2-hydroxy-1-oxa-8-azaspiro[4.5]decane-8-carboxylic acid *tert*-butyl ester (**Preparation 11**) using a method similar to that described for Examples 52 and 53 to afford a mixture of (E)- and (Z)- 4-hydroxy-4-[4-(2-methylpyridin-4-yl)but-3-enyl]piperidine-1-carboxylic acid *tert*-butyl ester: RT = 2.37 min;  $m/z$  ( $\text{ES}^+$ ) = 347.3  $[\text{M} + \text{H}]^+$ . A sample of this mixture of olefins was dissolved in EtOH and hydrogenated over a Pd catalyst, using a similar procedure to that described in Example 56, to give the title compound: RT = 2.32 min;  $m/z$  ( $\text{ES}^+$ ) = 349.3  $[\text{M} + \text{H}]^+$ .

The biological activity of representative compounds of the invention was tested in the following assay systems:

#### Yeast Reporter Assay

The yeast cell-based reporter assays have previously been described in the literature (e.g. see Miret J. J. et al, 2002, J. Biol. Chem., 277:6881-6887; Campbell R.M. et al, 1999, Bioorg. Med. Chem. Lett., 9:2413-2418; King K. et al, 1990, Science, 250:121-123); WO

99/14344; WO 00/12704; and US 6,100,042). Briefly, yeast cells have been engineered such that the endogenous yeast G-alpha (GPA1) has been deleted and replaced with G-protein chimeras constructed using multiple techniques. Additionally, the endogenous yeast alpha-cell GPCR, Ste3 has been deleted to allow for a homologous expression of a mammalian GPCR of choice. In the yeast, elements of the pheromone signaling transduction pathway, which are conserved in eukaryotic cells (for example, the mitogen-activated protein kinase pathway), drive the expression of Fus1. By placing  $\beta$ -galactosidase (LacZ) under the control of the Fus1 promoter (Fus1p), a system has been developed whereby receptor activation leads to an enzymatic read-out.

Yeast cells were transformed by an adaptation of the lithium acetate method described by Agatep et al, (Agatep, R. et al, 1998, Transformation of *Saccharomyces cerevisiae* by the lithium acetate/single-stranded carrier DNA/polyethylene glycol (LiAc/ss-DNA/PEG) protocol. Technical Tips Online, Trends Journals, Elsevier). Briefly, yeast cells were grown overnight on yeast tryptone plates (YT). Carrier single-stranded DNA (10 $\mu$ g), 2 $\mu$ g of each of two Fus1p-LacZ reporter plasmids (one with URA selection marker and one with TRP), 2 $\mu$ g of GPR1 16 (human or mouse receptor) in yeast expression vector (2 $\mu$ g origin of replication) and a lithium acetate/ polyethylene glycol/ TE buffer was pipetted into an Eppendorf tube. The yeast expression plasmid containing the receptor/ no receptor control has a LEU marker. Yeast cells were inoculated into this mixture and the reaction proceeds at 30°C for 60min. The yeast cells were then heat-shocked at 42°C for 15min. The cells were then washed and spread on selection plates. The selection plates are synthetic defined yeast media minus LEU, URA and TRP (SD-LUT). After incubating at 30°C for 2-3 days, colonies that grow on the selection plates were then tested in the LacZ assay.

In order to perform fluorimetric enzyme assays for  $\beta$ -galactosidase, yeast cells carrying the human or mouse GPR1 16 receptor were grown overnight in liquid SD-LUT medium to an unsaturated concentration (i.e. the cells were still dividing and had not yet reached stationary phase). They were diluted in fresh medium to an optimal assay concentration and 90 $\mu$ l of yeast cells are added to 96-well black polystyrene plates (Costar). Compounds, dissolved in DMSO and diluted in a 10% DMSO solution to 10X concentration, were added to the plates and the plates placed at 30°C for 4h. After 4h, the substrate for the  $\beta$ -galactosidase was added to each well. In these experiments, Fluorescein di ( $\beta$ -D-galactopyranoside) was used (FDG), a substrate for the enzyme that releases fluorescein, allowing a fluorimetric read-out. 20 $\mu$ l per well of 500 $\mu$ M FDG/2.5% Triton X100 was added (the detergent was necessary to render the cells permeable). After incubation of the cells with the substrate for 60min, 20 $\mu$ l per well of 1M sodium carbonate was added to terminate the reaction and enhance the fluorescent signal. The plates were then read in a fluorimeter at 485/535nm.

The compounds of the invention give an increase in fluorescent signal of at least ~ 1.5-fold that of the background signal (i.e. the signal obtained in the presence of 1% DMSO without compound). Compounds of the invention which give an increase of at least 5-fold may be preferred.

#### cAMP Assay

A stable cell line expressing recombinant human GPR1 16 was established and this cell line was used to investigate the effect of compounds of the invention on intracellular levels of

cyclic AMP (cAMP). The cells monolayers were washed with phosphate buffered saline and stimulated at 37°C for 30min with various concentrations of compound in stimulation buffer plus 1% DMSO. Cells were then lysed and cAMP content determined using the Perkin Elmer AlphaScreen™ (Amplified Luminescent Proximity Homogeneous Assay) cAMP kit. Buffers and assay conditions were as described in the manufacturer's protocol. Compounds of the invention showed a concentration-dependant increase in intracellular cAMP level.

Compounds of the invention showed a concentration-dependant increase in intracellular cAMP level and generally had an EC<sub>50</sub> of <10µM. Compounds showing an EC<sub>50</sub> of less than 1µM in the cAMP assay may be preferred.

#### **In vivo feeding study**

The effect of compounds of the invention on body weight and food and water intake may be examined in freely-feeding male Sprague-Dawley rats maintained on reverse-phase lighting. Test compounds and reference compounds are dosed by appropriate routes of administration (e.g. intraperitoneally or orally) and measurements made over the following 24 h. Rats are individually housed in polypropylene cages with metal grid floors at a temperature of 21±4°C and 55±20% humidity. Polypropylene trays with cage pads are placed beneath each cage to detect any food spillage. Animals are maintained on a reverse phase light-dark cycle (lights off for 8 h from 09.30-17.30 h) during which time the room was illuminated by red light. Animals have free access to a standard powdered rat diet and tap water during a two week acclimatization period. The diet is contained in glass feeding jars with aluminum lids. Each lid has a 3-4 cm hole in it to allow access to the food. Animals, feeding jars and water bottles are weighed (to the nearest 0.1 g) at the onset of the dark period. The feeding jars and water bottles are subsequently measured 1, 2, 4, 6 and 24 h after animals are dosed with a compound of the invention and any significant differences between the treatment groups at baseline compared to vehicle-treated controls.

Selected compounds of the invention showed a statistically significant hypophagic effect at one or more time points at a dose of ≤ 100mg/kg.

#### **Anti-diabetic effects of compounds of the invention in an in-vitro model of pancreatic beta cells (HIT-T15)**

##### Cell Culture

HIT-T15 cells (passage 60) were obtained from ATCC, and were cultured in RPMI1640 medium supplemented with 10% fetal calf serum and 30nM sodium selenite. All experiments were done with cells at less than passage 70, in accordance with the literature, which describes altered properties of this cell line at passage numbers above 81 (Zhang HJ, Walseth TF, Robertson RP. Insulin secretion and cAMP metabolism in HIT cells. Reciprocal and serial passage-dependent relationships. *Diabetes*. 1989 Jan;38(1):44-8).

##### cAMP assay

HIT-T15 cells were plated in standard culture medium in 96-well plates at 100,000 cells/ 0.1ml/ well and cultured for 24 hr and the medium was then discarded. Cells were incubated for 15min at room temperature with 100µl stimulation buffer (Hanks buffered salt solution, 5mM HEPES, 0.5mM IBMX, 0.1% BSA, pH 7.4). This was discarded and replaced

with compound dilutions over the range 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30  $\mu\text{M}$  in stimulation buffer in the presence of 0.5% DMSO. Cells were incubated at room temperature for 30min. Then 75 $\mu\text{l}$  lysis buffer (5mM HEPES, 0.3% Tween-20, 0.1% BSA, pH 7.4) was added per well and the plate was shaken at 900 rpm for 20 min. Particulate matter was removed by centrifugation at 3000rpm for 5min, then the samples were transferred in duplicate to 384-well plates, and processed following the Perkin Elmer AlphaScreen cAMP assay kit instructions. Briefly 25 $\mu\text{l}$  reactions were set up containing 8 $\mu\text{l}$  sample, 5 $\mu\text{l}$  acceptor bead mix and 12 $\mu\text{l}$  detection mix, such that the concentration of the final reaction components is the same as stated in the kit instructions. Reactions were incubated at room temperature for 150min, and the plate was read using a Packard Fusion instrument. Measurements for cAMP were compared to a standard curve of known cAMP amounts (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30, 100, 300, 1000 nM) to convert the readings to absolute cAMP amounts. Data was analysed using XLfit 3 software.

Representative compounds of the invention were found to increase cAMP at an  $\text{EC}_{50}$  of less than 10  $\mu\text{M}$ . Compounds showing an  $\text{EC}_{50}$  of less than 1  $\mu\text{M}$  in the cAMP assay may be preferred.

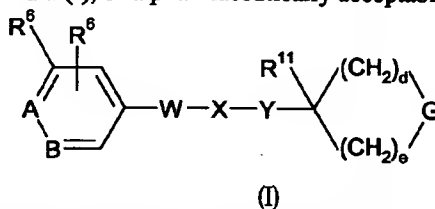
#### Insulin secretion assay

HIT-T 15 cells were plated in standard culture medium in 12-well plates at 106 cells/ 1 ml/ well and cultured for 3 days and the medium was then discarded. Cells were washed x 2 with supplemented Krebs-Ringer buffer (KRB) containing 119 mM NaCl, 4.74 mM KCl, 2.54 mM  $\text{CaCl}_2$ , 1.19 mM  $\text{MgSO}_4$ , 1.19 mM  $\text{KH}_2\text{PO}_4$ , 25 mM  $\text{NaHCO}_3$ , 10mM HEPES at pH 7.4 and 0.1% bovine serum albumin. Cells were incubated with 1ml KRB at 37°C for 30 min which was then discarded. This was followed by a second incubation with KRB for 30 min, which was collected and used to measure basal insulin secretion levels for each well. Compound dilutions (0, 0.1, 0.3, 1, 3, 10  $\mu\text{M}$ ) were then added to duplicate wells in 1ml KRB, supplemented with 5.6 mM glucose. After 30 min incubation at 37°C samples were removed for determination of insulin levels. Measurement of insulin was done using the Mercodia Rat insulin ELISA kit, following the manufacturers instructions, with a standard curve of known insulin concentrations. For each well insulin levels were subtracted by the basal secretion level from the pre-incubation in the absence of glucose. Data was analysed using XLfit 3 software.

Representative compounds of the invention were found to increase insulin secretion at an  $\text{EC}_{50}$  of less than 10  $\mu\text{M}$ . Compounds showing an  $\text{EC}_{50}$  of less than 1  $\mu\text{M}$  in the insulin secretion assay may be preferred.

## WHAT IS CLAIMED IS:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



wherein one of A and B is nitrogen and the other is CR<sup>1</sup>;

W and Y are independently a bond, an unbranched or a branched C<sub>1-3</sub> alkylene or an unbranched or a branched C<sub>2-3</sub> alkenylene;

X is selected from CH<sub>2</sub>, O, S, CH(OH), CH(halogen), C(O), C(O)O, C(O)S, SC(O), C(O)CH<sub>2</sub>S, C(O)CH<sub>2</sub>C(OH), C(O)CH<sub>2</sub>C(O), OC(O), NR<sup>5</sup>, CH(NR<sup>5</sup>R<sup>55</sup>), C(O)NR<sup>2</sup>, S(O) and S(O)<sub>2</sub>;

G is CHR<sup>3</sup>, N-C(O)OR<sup>4</sup>, N-C(O)NR<sup>4</sup>R<sup>5</sup>, N-C<sup>alkylene</sup>-C<sup>OR</sup><sup>4</sup>, N-C(O)C(O)OR<sup>4</sup>, N-S(O)<sub>2</sub>R<sup>4</sup>, N-C(O)R<sup>4</sup> or N-P(O)(O-Ph)<sub>2</sub>; or N-heterocyclyl or N-heteroaryl, either of which may optionally be substituted by one or two groups selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy or halogen;

R<sup>1</sup> is hydrogen, halogen, cyano, C(O)NH<sub>2</sub>, C<sub>1-4</sub>alkyl, SO<sub>2</sub>C<sub>1-4</sub>alkyl, SOC<sub>1-4</sub>alkyl or SC<sub>1-4</sub>alkyl;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub>alkyl;

R<sup>3</sup> is C<sub>3-6</sub>alkyl;

R<sup>4</sup> is C<sub>1-8</sub>alkyl, C<sub>2-8</sub>alkenyl or C<sub>2-8</sub>alkynyl, any of which may be optionally substituted by one or more halo atoms, NR<sup>5</sup>R<sup>55</sup>, OR<sup>5</sup>, C(O)OR<sup>5</sup>, OC(O)R<sup>5</sup> or cyano, and may contain a CH<sub>2</sub> group that is replaced by O or S; or a C<sub>3-7</sub>cycloalkyl, aryl, heterocyclyl, heteroaryl, C<sub>1-4</sub>alkyleneC<sub>3-7</sub>cycloalkyl, C<sub>1-4</sub>alkylenearyl, C<sub>1-4</sub>alkyleneheterocyclyl or C<sub>1-4</sub>alkyleneheteroaryl, any of which may be substituted with one or more substituents selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>fluoroalkyl, OR<sup>5</sup>, CN, NR<sup>5</sup>R<sup>55</sup>, SO<sub>2</sub>Me, NO<sub>2</sub> or C(O)OR<sup>5</sup>;

R<sup>5</sup> and R<sup>55</sup> are independently hydrogen or C<sub>1-4</sub>alkyl; or taken together R<sup>5</sup> and R<sup>55</sup> may form a 5 or 6 membered heterocyclic ring;

R<sup>6</sup> is hydrogen, halogen, CN, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, ethynyl, C(O)NR<sup>7</sup>R<sup>77</sup> or C<sub>1-4</sub>alkyleneS(O)<sub>f</sub>;

R<sup>7</sup> and R<sup>77</sup> are independently hydrogen or C<sub>1-4</sub>alkyl; or taken together R<sup>7</sup> and R<sup>77</sup> may form a 5 or 6 membered heterocyclic ring;

R<sup>8</sup> is hydrogen, halogen, CN, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy;

R<sup>11</sup> is hydrogen or hydroxy;

d is 0, 1, 2 or 3;

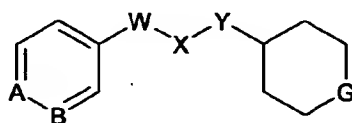
e is 1, 2, 3, 4 or 5;

with the proviso that d + e is 2, 3, 4 or 5; and

f is 0, 1 or 2.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein A is nitrogen.

3. A compound according to either claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein  $R^1$  is  $C_{1-4}$  alkyl, hydrogen or cyano.
4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein  $R^6$  is hydrogen, methyl or halogen.
5. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein G is  $N-C(O)OR^4$ ,  $N-C(O)NR^4R^5$  or N-heteroaryl.
6. A compound according to claim 5, or a pharmaceutically acceptable salt thereof, wherein G is  $N-C(O)OR^4$ .
7. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein  $R^4$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl or  $C_{2-8}$  alkynyl optionally substituted by one or more halo atoms or cyano, which may contain a  $CH_2$  group that may be replaced by O or S; or a  $C_{3-7}$  cycloalkyl, aryl or  $d^{\wedge}$ alkyleneCs $^{\wedge}$ cycloalkyl, any of which may be substituted with one or more substituents selected from halo,  $C_{1-4}$  alkyl,  $C_{1-4}$  fluoroalkyl,  $OR^5$ , CN,  $NR^5R^{55}$ ,  $NO_2$  or  $C(O)OC_{1-4}$ alkyl.
8. A compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein  $R^4$  represents  $C_{1-8}$  alkyl,  $C_{2-8}$  alkenyl or  $C_{2-8}$  alkynyl optionally substituted by one or more halo atoms or cyano, which may contain a  $CH_2$  group that may be replaced by O or S; or a  $C_{3-7}$  cycloalkyl which may be substituted with one or more substituents selected from halo,  $C_{1-4}$  alkyl,  $C_{1-4}$  fluoroalkyl,  $OR^5$ , CN,  $NR^5R^{55}$ ,  $NO_2$  or  $C(O)OC_{1-4}$ alkyl.
9. A compound according to claim 7 or 8, or a pharmaceutically acceptable salt thereof, wherein the group represented by  $R^4$  is unsubstituted.
10. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein d and e each represent 1.
11. A compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein d and e each represent 2.
12. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein when W is  $C_{2-3}$  alkenylene, the stereochemistry at the double bond is (*E*).
13. A compound according to any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein -W-X-Y- represents a 4 or 5 atom chain.
14. A compound according to claim 1 which is of formula (Ia), or a pharmaceutically acceptable salt thereof:



(Ia)

wherein one of A and B is nitrogen and the other is CR<sup>1</sup>;

W and Y are independently a bond, C<sub>1-3</sub>alkylene or C<sub>2-3</sub>alkenylene;

X is selected from CH<sub>2</sub>, O, S, CO, CO<sub>2</sub>, COS, SCO, COCH<sub>2</sub>S, COCH<sub>2</sub>CO, OCO, CONR<sup>2</sup>, SO and SO<sub>2</sub>;

G is CHR<sup>3</sup>, NCOOR<sup>4</sup>, or NCONR<sup>4</sup>R<sup>5</sup>;

R<sup>1</sup> is hydrogen, halogen, cyano or C<sub>1-4</sub>alkyl;

R<sup>2</sup> is C<sub>1-4</sub>alkyl;

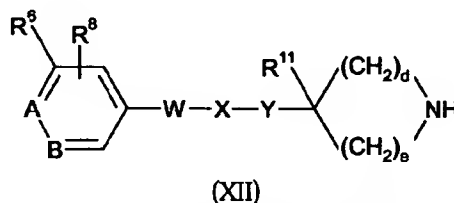
R<sup>3</sup> is C<sub>3-6</sub>alkyl;

R<sup>4</sup> is C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl optionally substituted by one or more fluoro atoms or cyano, C<sub>3-7</sub>cycloalkyl, or aryl optionally substituted with C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halogen, CF<sub>3</sub>, nitro, cyano, or CO<sub>2</sub>C<sub>1-4</sub>alkyl; and

R<sup>5</sup> is hydrogen or C<sub>1-4</sub>alkyl.

15. A compound of formula (I) as defined in any one of Examples 1 to 136, or a pharmaceutically acceptable salt thereof.
16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
17. A method for the treatment of a disease or condition in which GPR116 plays a role comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.
18. A method for the regulation of satiety comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.
19. A method for the treatment of obesity comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.
20. A method for the treatment of diabetes comprising a step of administering to a subject in need thereof an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.
21. A method for the treatment of metabolic syndrome (syndrome X), impaired glucose tolerance, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels or hypertension comprising a step of administering to a patient in need thereof an effective amount of a compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.

22. A compound of formula (XII):



wherein one of A and B is nitrogen and the other is CR<sup>1</sup>;

W and Y are independently a bond, an unbranched or a branched C<sub>1-3</sub> alkylene or an unbranched or a branched C<sub>2-3</sub> alkenylene;

X is selected from CH<sub>2</sub>, O, S, CH(OH), CH(halogen), C(O), C(O)O, C(O)S, SC(O), C(O)CH<sub>2</sub>S, C(O)CH<sub>2</sub>C(OH), C(O)CH<sub>2</sub>C(O), OC(O), NR<sup>5</sup>, CH(NR<sup>5</sup>R<sup>55</sup>), C(O)NR<sup>2</sup>, S(O) and S(O)<sub>2</sub>;

R<sup>1</sup> is hydrogen, halogen, cyano, C(O)NH<sub>2</sub>, C<sub>1-4</sub>alkyl, SO<sub>2</sub>C<sub>1-4</sub>alkyl, SOC<sub>1-4</sub>alkyl or SC<sub>1-4</sub>alkyl;

R<sup>2</sup> is hydrogen or C<sub>1-4</sub>alkyl;

R<sup>5</sup> and R<sup>55</sup> are independently hydrogen or C<sub>1-4</sub>alkyl; or taken together R<sup>5</sup> and R<sup>55</sup> may form a 5 or 6 membered heterocyclic ring;

R<sup>6</sup> is hydrogen, halogen, CN, C<sub>1-4</sub>alkyl, C<sup>^</sup>alkoxy, ethynyl, C(O)NR<sup>7</sup>R<sup>77</sup> or C<sub>1-4</sub>alkyleneS(O)<sub>f</sub>;

R<sup>7</sup> and R<sup>77</sup> are independently hydrogen or C<sub>1-4</sub>alkyl; or taken together R<sup>7</sup> and R<sup>77</sup> may form a 5 or 6 membered heterocyclic ring;

R<sup>8</sup> is hydrogen, halogen, CN, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy;

R<sup>11</sup> is hydrogen or hydroxy;

d is 0, 1, 2 or 3;

e is 1, 2, 3, 4 or 5;

with the proviso that d + e is 2, 3, 4 or 5; and

f is 0, 1 or 2.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2005/050264

A. CLASSIFICATION A61K31/44 C07D401/12 A61P3/04 A61P3/10		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document with indication where appropriate, of the relevant passages	Relevant to claim No
P, X	WO 2005/007647 A (ARENA PHARMACEUTICALS, INC; JONES, ROBERT, M; SEMPLE, GRAEME; XIONG, Y) 27 January 2005 (2005-01-27) claim 1	1-22
P, X	WO 2005/121121 A (ARENA PHARMACEUTICALS, INC; JONES, ROBERT, M; SEMPLE, GRAEME; XIONG, Y) 22 December 2005 (2005-12-22) claim 1	1-22
P <sub>5</sub> X	WO 2005/061489 A (PROSIDION LIMITED; FYFE, MATTHEW; GARDNER, LISA; KING-UNDERWOOD, JOHN;) 7 July 2005 (2005-07-07) cited in the application claim 1	1-22
- / - -		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
* Special categories of cited documents "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search 28 February 2006		Date of mailing of the international search report 07/03/2006
Name and mailing address of the ISA/ European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl Fax (+31-70) 340-3016		Authorized officer Beri I lon, L

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2005/050264

\*Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/065380 A (ARENA PHARMACEUTICALS INC; JONES, ROBERT, M; SEMPLE, SRAEME; FIORAVANT) 5 August 2004 (2004-08-05) claim 1 -----	1-22

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/GB2005/050264

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 ☒ Claims Nos 17-21  
because they relate to subject matter not required to be searched by this Authority, namely  
Although claims 17-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
- 2 ☐ Claims Nos  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically
- 3 ☐ Claims Nos  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

- 1 ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims
- 2 ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
- 3 ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos
- 4 ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest
- ☐ No protest accompanied the payment of additional search fees

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No  
PCT/GB2005/050264

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005007647 A	27-01-2005	AU 2004257261 A1	27-01-2005
WO 2005121121 A	22-12-2005	NONE	
WO 2005061489 A	07-07-2005	NONE	
WO 2004065380 A	05-08-2004	AU 2004205642 A1	05-08-2004
		BR 0406761 A	20-12-2005
		CA 2512899 A1	05-08-2004
		EP 1599468 A1	30-11-2005
		HR 20050696 A2	31-12-2005